Biochemical and Biophysical Research Communications 402 (2010) 7–13

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

High-salt diet advances molecular circadian rhythms in mouse peripheral tissues

Hideaki Oike [a,*], Kanji Nagai [a,b], Tatsunobu Fukushima [b], Norio Ishida [c,d], Masuko Kobori [a]

[a] Food Function Division, National Food Research Institute (NFRI), National Agriculture and Food Research Organization (NARO), Tsukuba, Ibaraki 305-8642, Japan
[b] Mitsubishi Rayon Company, Ltd., Yokohama, Kanagawa 230-0053, Japan
[c] Ishida Group of Clock Gene, Biomedical Research Institute, National Institute of Advanced Industrial Science and Technology (AIST), Tsukuba, Ibaraki 305-8566, Japan
[d] Graduate School of Life and Environmental Sciences, University of Tsukuba, Ibaraki 305-8572, Japan

ARTICLE INFO

Article history:
Received 6 September 2010
Available online 1 October 2010

Keywords:
Circadian clocks
Food entrainment
Glucose transporters
Focused DNA microarray
High-salt diet

ABSTRACT

Dietary compounds influence the expression of various genes and play a major role in changing physiological and metabolic states. However, little is known about the role of food ingredients in the regulation of circadian gene expression. Here, we show that feeding mice with a high-salt (HS) diet *ad libitum* for over 2 weeks advanced the phase of clock gene expression by about 3 h in the liver, kidney, and lung, but did not change circadian feeding, drinking, and locomotor rhythms. Focused DNA microarray analysis showed that the expression phase of many genes related to metabolism in the liver was also advanced. Immediately before phase advancement in peripheral tissues, the mRNA expression of sodium–glucose cotransporter 1 (*Sglt1*) and glucose transporter 2 (*Glut2*), that are responsible for glucose absorption, was increased in the jejunum. Furthermore, blood glucose uptake increased more rapidly after consuming the HS diet than the control diet. Moreover, phloridzin, a specific inhibitor of SGLT1, prevented the increased glucose transporter expression in the jejunum and phase advancement in the livers of mice on the HS diet. These results suggest that increased glucose absorption induced by dietary HS alters the food entrainment of peripheral molecular circadian rhythms.

1. Introduction

The mammalian circadian clock comprises a central pacemaker in the suprachiasmatic nucleus (SCN) of the hypothalamus and various oscillators in most peripheral tissues. The molecular oscillator of the circadian clock is thought to depend on a negative transcriptional feedback loop involving clock genes such as *Per*, *Cry*, *Clock*, and *Bmal* [1]. Although light–dark (LD) cycles comprise a critical cue for the central clock, cyclic feeding behavior is the predominant cue for many peripheral tissue clocks [2,3]. Restricted daytime feeding by nocturnal animals obviously shifts their peripheral clocks [4,5]. Specific nutritional diets such as high-fat and ketogenic diets affect circadian oscillators despite feeding *ad libitum* [6,7], suggesting that food quality and not simply the timing of caloric intake, is also a factor in the entrainment of circadian clocks. These diets affect the metabolic status of mice, and probably alter their circadian clocks. However, whether food ingredients affect circadian clocks in other ways such as by influencing nutritional absorption or sensing systems remains unclear.

Diet primarily regulates the glucose transport system in the small intestine [8]. A low-sodium diet decreases expression of the sodium–glucose cotransporter 1 (*Sglt1*) in chickens, and a high-fructose diet increases the expression of glucose transporters *Glut2* and *Glut5* in mice and rats. Dietary salt and sugar influence glucose absorption in the small intestine as well as plasma sugar levels, and play a vital role in nutrition. Nutritional absorption through the small intestine might be indispensable for the food entrainment of peripheral clocks because jejunal resection attenuates daily corticosterone rhythms in the blood [9]. Thus, some food ingredients such as sodium and sugars might influence nutritional absorption and the food entrainment of circadian clocks.

We tested this hypothesis by investigating the effects of a high-salt diet on activity, feeding, and drinking patterns in mice, as well as on the cyclic expression of clock genes and their downstream clock-control targets.

2. Materials and methods

2.1. Animals and treatments

Animals were treated in accordance with the basic guidelines set forth by the Ministry of Agriculture, Forestry, and Fisheries for laboratory animal studies. The animal studies were approved by the review board of Animal Ethics of the National Food Research

Abbreviations: HS, high-salt; NS, normal salt.

* Corresponding author. Address: Food Function Division, National Food Research Institute (NFRI), National Agriculture and Food Research Organization (NARO), 2-1-12 Kannondai, Tsukuba, Ibaraki 305-8642, Japan. Fax: +81 29 838 8041.
E-mail address: oike@affrc.go.jp (H. Oike).

0006-291X/$ - see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.bbrc.2010.09.072

Institute. Young adult male BALB/cAn mice were housed under 12 h light/dark photocycles (light period from 08:00 to 20:00), fed an NS diet (0.3% NaCl; F2Dahl-0.3) or an HS diet (4.0% NaCl; F2Dahl-4.0) (Oriental Yeast Co., Tokyo, Japan).

2.2. Quantitative RT-PCR analysis

Total RNA was prepared from the liver, kidneys, lungs, and jejunum tissues at ZT5 (Zeitgeber Time; onset of a light period is ZT0) for single time point analysis, and at ZT1, 5, 9, 13, 17, and 21 for the 24-h study. For the real-time PCR procedure, gene-specific primers and SYBR Green Real-Time PCR Master Mix-Plus (Toyobo, Osaka, Japan) were used and products detected by the ABI Prism 7000 Genetic Analyzer (Applied Biosystems, CA, USA). The relative amount of each transcript was normalized to the amount of GAPDH transcript in the same cDNA.

2.3. DNA microarray analysis

DNA microarray analysis, using the fibrous DNA chip Genopal® (Mitsubishi Rayon, Tokyo, Japan), was performed as previously described [10]. DNA oligonucleotide probes were synthesized for the detection of 206 metabolic genes. Total RNA was extracted from the livers of mice fed on the NS or HS diet for 4 weeks. Hybridization, washing, and fluorescent-labeling was performed by Genopal® instrument systems (UE-104; Mitsubishi Rayon). Hybridization signal acquisition was performed using a DNA microarray reader, adopting multibeam excitation technology (Yokogawa Electric Co., Tokyo, Japan). The relative amount of each transcript was normalized to the amount of GAPDH transcript in the same cDNA.

2.4. Behavioral analyses

Mice were monitored in cages with combined feeding, drinking, and activity sensors simultaneously for 5-min durations in each animal. (FDM 300; Melquest, Toyama, Japan). Mice were fed an NS diet for 2 weeks, an HS diet for 4 weeks, then the NS diet for 2 weeks. Data analysis was performed using Feedam software (Melquest).

2.5. Measurement of blood glucose after re-feeding

Mice were fed on the NS or HS diet for 8 days and then fasted overnight, followed by re-feeding the diet for 30 min. Blood glucose was measured just before re-feeding (0 min), and after 30, 50, 70, 90, 120, and 180 min using a blood glucose test meter (Arkray Inc., Kyoto, Japan), sampling from the tail vein.

2.6. Statistical analysis

All values are expressed as means ± SEM. The difference in degree of expression was statistically evaluated using the Student's *t*-test, while time-dependence of gene expression was evaluated

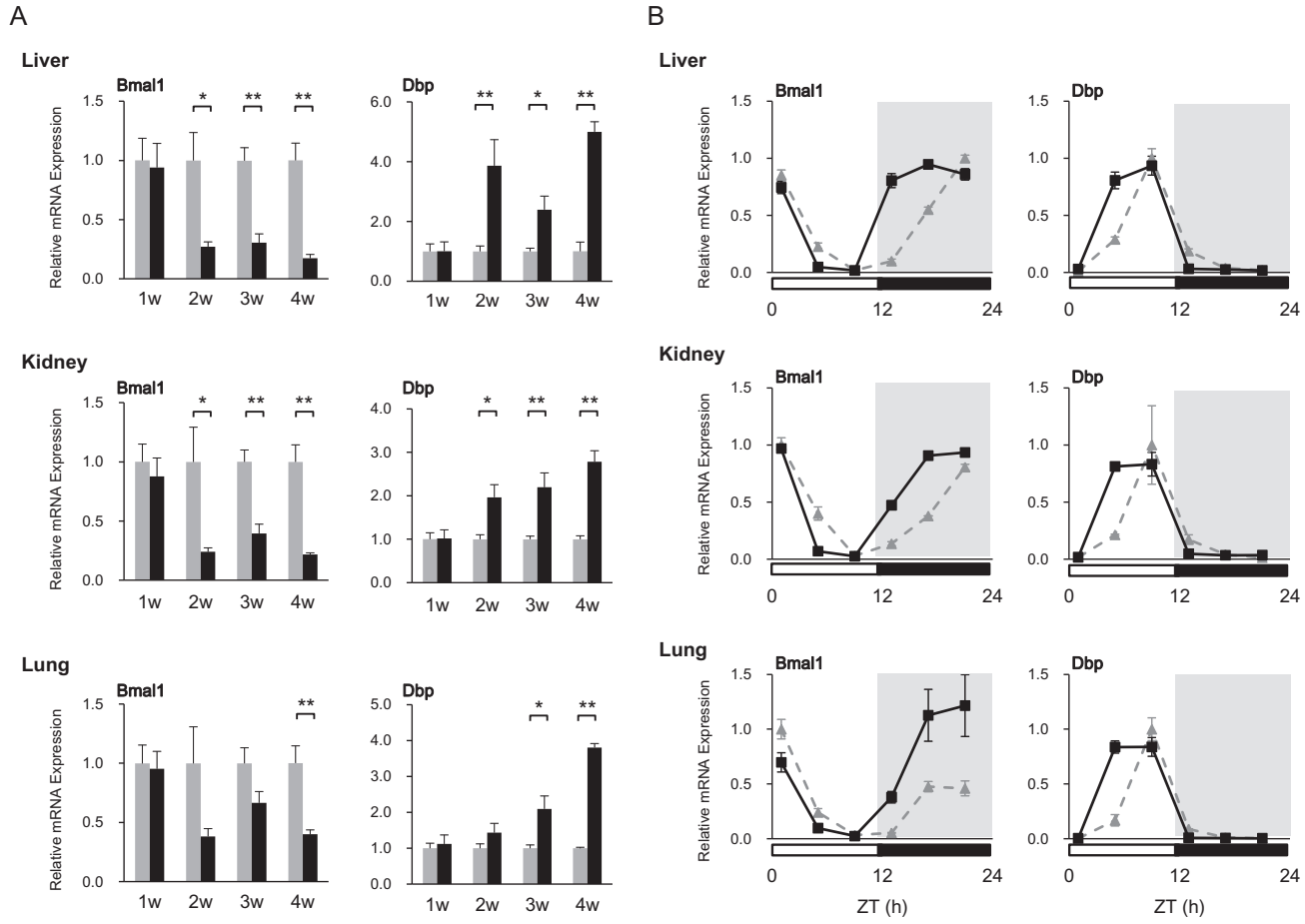

Fig. 1. High-salt diet alters *Bmal1* and *Dbp* clock gene expression in the liver, kidneys, and lungs. (A) Transcripts of *Bmal1* (left panels) and *Dbp* (right panels) at ZT5 in liver, kidneys, and lungs of mice fed with normal (NS, 0.3% NaCl; gray bars) or high (HS, 4.0% NaCl; black bars) salt diets measured by quantitative RT-PCR every week for 4 weeks. Data are shown as means ± SEM (week 1, $n = 9$; weeks 2 and 3; $n = 6$; week 4, $n = 3$). Significant differences for comparisons between NS and HS diets are indicated as $^{*}p < 0.05$ and $^{**}p < 0.01$. (B) Temporal expression of *Bmal1* and *Dbp* mRNA in the liver, kidneys, and lungs of mice fed with NS (gray dotted lines) or HS (black solid lines) diets for 4 weeks analyzed by quantitative RT-PCR. Means ± SEM ($n = 3$). Horizontal open and solid bars indicate day and night, respectively.

Table 1
Cosinor analysis of *Bmal1* and *Dbp* mRNAs in mice fed with NS or HS diet.

	Gene	Dietary salt	MESOR	Amplitude	Acrophase (h)
Liver	*Bmal1*	Normal	0.46 ± 0.04	0.48 ± 0.06	23.2 ± 0.5
		High	0.56 ± 0.08	0.54 ± 0.11	20.3 ± 0.8*
	Dbp	Normal	0.21 ± 0.14	0.38 ± 0.20	8.8 ± 2.0
		High	0.28 ± 0.11	0.48 ± 0.16	7.0 ± 1.3
Kidney	*Bmal1*	Normal	0.46 ± 0.03	0.52 ± 0.04	21.9 ± 0.3
		High	0.57 ± 0.08	0.50 ± 0.12	18.8 ± 0.9*
	Dbp	Normal	0.26 ± 0.12	0.40 ± 0.16	8.8 ± 1.6
		High	0.31 ± 0.11	0.49 ± 0.16	7.2 ± 1.3
Lung	*Bmal1*	Normal	0.38 ± 0.10	0.40 ± 0.14	23.1 ± 1.3
		High	0.59 ± 0.03	0.66 ± 0.04	19.8 ± 0.2
	Dbp	Normal	0.24 ± 0.13	0.38 ± 0.18	8.9 ± 1.8
		High	0.30 ± 0.11	0.45 ± 0.15	7.1 ± 1.3

Data shown in Fig. 1B analyzed using cosinor method. MESOR, mean statistics of rhythm; amplitude, one-half the total peak-trough variation; acrophase, hours delay from ZT0 (lights on). Values are means ± SEM ($n = 3$).
* $p < 0.05$ (vs. normal salt).

using one-way ANOVA. A $p < 0.05$ indicated a statistically significant difference. Circadian rhythms were statistically analyzed using the modified cosinor method (nonlinear least-squares [NLLS] Marquardt–Levenberg algorithm) [11].

3. Results

3.1. Expression rhythm of clock genes in mice peripheral tissues were advanced by HS diet

We examined the expression of the clock genes *Bmal1* and *Dbp* in mice fed with a normal salt (NS; 0.3% NaCl) diet or a high-salt (HS; 4.0% NaCl) diet for 4 weeks at Zeitgeber time 5 (ZT5; ZT0 was defined as the time of lights on). The HS diet caused *Bmal1* expression to decline from week 2 in the liver and kidneys and from week 4 in the lungs (Fig. 1A). In contrast, *Dbp* expression significantly increased from week 2 in the liver and kidneys and from week 3 in the lungs. Body weight did not differ between groups throughout the study period (Supplementary Fig. 1A).

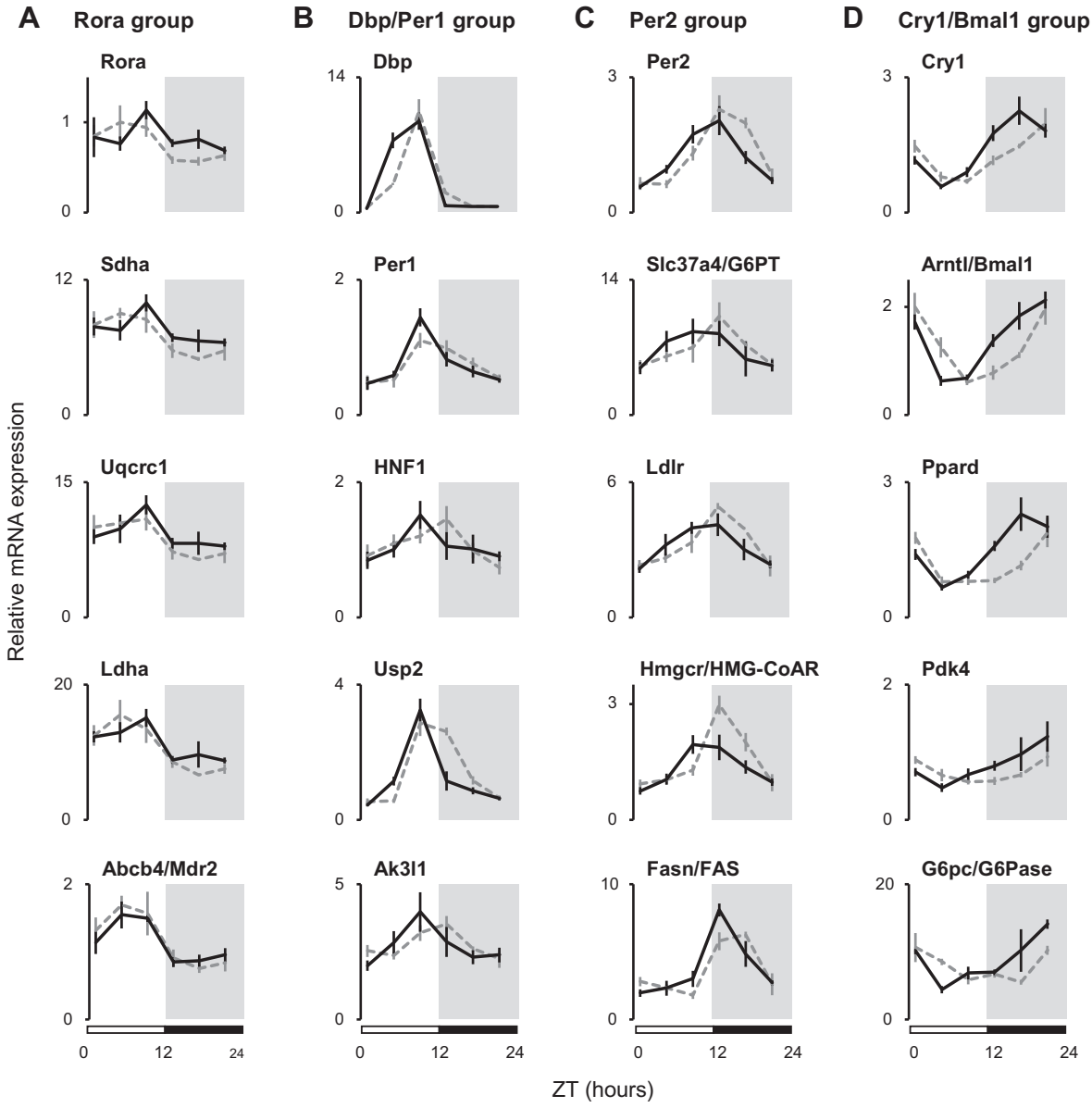

Fig. 2. Effect of HS diet on phase of rhythmic gene expression in the liver. Temporal expression of representative genes related to liver metabolism in mice fed with NS (gray dotted lines) or HS (black solid lines) diets for 4 weeks analyzed using focused DNA chip (Genopal®). Genes were classified into groups A–D based upon time of peak expression of NS diet group. Data are shown as means ± SEM ($n = 3$). Horizontal open and solid bars indicate day and night, respectively.

We investigated the 24-h gene expression profile of *Bmal1* and *Dbp* on week 4 (Fig. 1B). Baseline and peak expression levels of the two clock genes were similar between the two groups, but their rhythmic phases differed. Cosinor analysis showed that the HS diet advanced the phase in all three tested tissues, from 1.6 to 1.8 h for *Dbp* and 2.9 to 3.3 h for *Bmal1* (Table 1).

3.2. Effects of HS diet on metabolic genes in liver

To further explore the effects of the HS diet on the rhythmic expression of transcripts, we also studied the 24-h expression profiles of the genes related to energy metabolism in the liver, many of which are controlled by clock genes [12]. The focused DNA microarray contained 206 metabolic genes including 18 clock genes. Microarray analysis of the control group detected the mRNA expression of 147 genes. The expression of 47 of them including 11 clock genes was rhythmic ($p < 0.05$, one-way ANOVA; Fig. 2 and Supplementary Table 1). The phase of many rhythmically expressed genes was advanced by the HS diet. We classified four subgroups within the NS group based on peak expression time. The Dbp/Per1 group (Fig. 2B) that phased in the latter half of the light period, included the *Hnf1a* (HNF1), *Usp2* (ubiquitin specific peptidase 2), and *Ak3l1* (adenylate kinase 3-like 1) genes. Phases were advanced by about 0.9 h in the HS group (Supplementary Table 1). Genes in the Per2 group (Fig. 2C) that were phased to the first half of the dark period included *Slc37a4* (G6pt), *Ldlr* (low density lipoprotein receptor), and *Fasn* (fatty acid synthase). The effect on phase advancement was more powerful in this (≈1.9 h), than in the Dbp/Per1 group. Genes in the Cry1/Bmal1 group (Fig. 1D) that phased to the latter half of the dark period included *Ppard* (peroxisome proliferator activated receptor delta), *Pdk4* (pyruvate dehydrogenase kinase 4), and *G6pc* (glucose-6-phosphatase). The phase advancement effect of the HS diet was the most powerful in the Cry1/Bmal1 group (≈3.8 h). Lastly, genes in the Rora group (Fig. 2A) phased to the first half of the light period included *Actb* (β-actin), and *Ldha* (lactate dehydrogenase A). The HS diet slightly delayed the phase of gene expression in this group.

We also noted that the HS diet advanced the expression rhythms of genes encoding specific rate-limiting enzymes namely, *G6pc* (gluconeogenesis; 4.5 h), *Fasn* (fatty acid synthesis; 1.9 h), *Hmgcr* (cholesterol biosynthesis; 2.0 h), *Cyp7a1* (bile acid synthesis; 2.3 h), and *Gys2* (glycogen synthesis; 1.9 h) (Fig. 2 and Supplementary Table 1). Because rate-limiting steps in various metabolic pathways are key sites of circadian control [13], the HS diet might advance liver metabolic functions associated with these genes.

3.3. Activity rhythms were not advanced by HS diet

We examined the effect of the HS diet on nocturnal food intake, drinking, and locomotor activity rhythms in mice. Absolute differences in the feeding, drinking, total food intake, and locomotor activity patterns were not evident during the 4-week period (Fig. 3 and Supplementary Fig. 1C), although fluid intake increased about 1.7-fold (Supplementary Fig. 1B). The results of the wheel-running study of locomotor activity were the same ($n = 8$, Supplementary Fig. 2A). Moreover, the mice were maintained under constant dark (DD) conditions and fed with the NS or HS diet for 4 weeks to compare period length (Supplementary Fig. 2B). The length of the free-running period for the HS group (23.7 ± 0.0 h; $n = 8$) was equivalent to the NS group (23.7 ± 0.0 h; $n = 8$). These results suggest that the HS diet did not alter the central clock, which dominates active-resting cycles.

3.4. Glucose absorption in the jejunum was increased by HS diet

We concluded that the HS diet affected the food entrainment process in peripheral clocks without affecting feeding behavior. We also assumed that the nutritional absorption system was affected before phase advancement occurred. To test this hypothesis, we examined the expression of sodium–glucose cotransporter 1 (*Sglt1*) and of glucose transporters, *Glut2* and *Glut5*, all of which are responsible for mediating jejuna sugar absorption. The mRNA expression of *Sglt1* and *Glut2* was increased by week 1 of the HS diet, compared with the NS diet, whereas *Glut5* mRNA did not significantly differ between the groups (Fig. 4A). Meanwhile, *Bmal1*

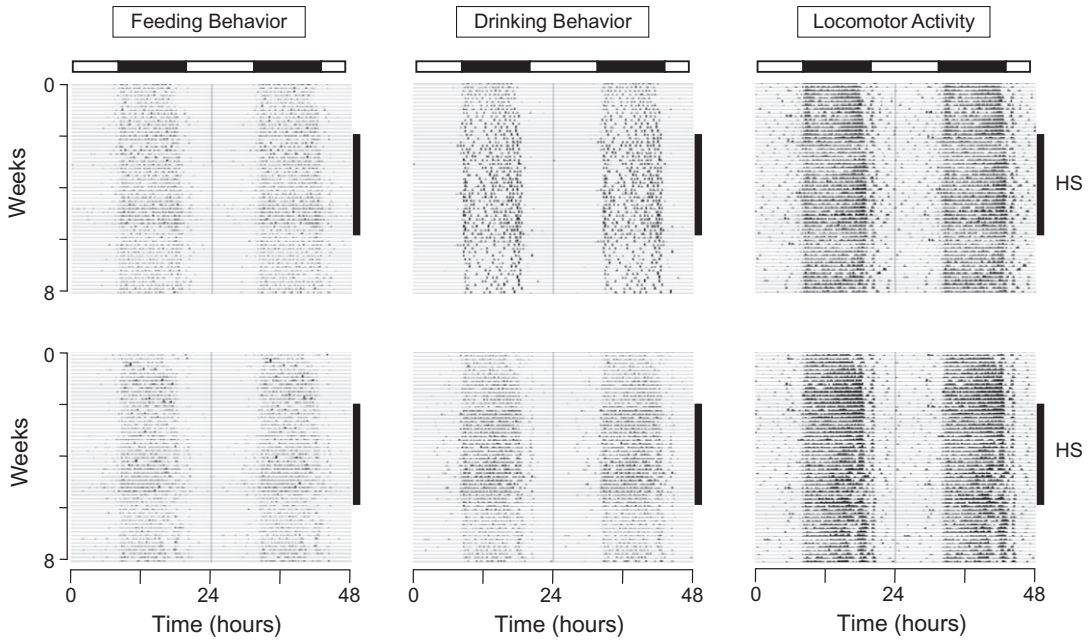

Fig. 3. High-salt diet does not alter circadian activities in mice. Feeding, drinking, and locomotor activities of mice. Representative data are from two animals. All animals ($n = 8$) were fed with NS diet for 2 weeks, HS diet for 4 weeks (shown as longitudinal black lines) and returned to NS diet for 2 weeks *ad libitum* on a 12:12 LD cycle (shown as horizontal open and solid bars).

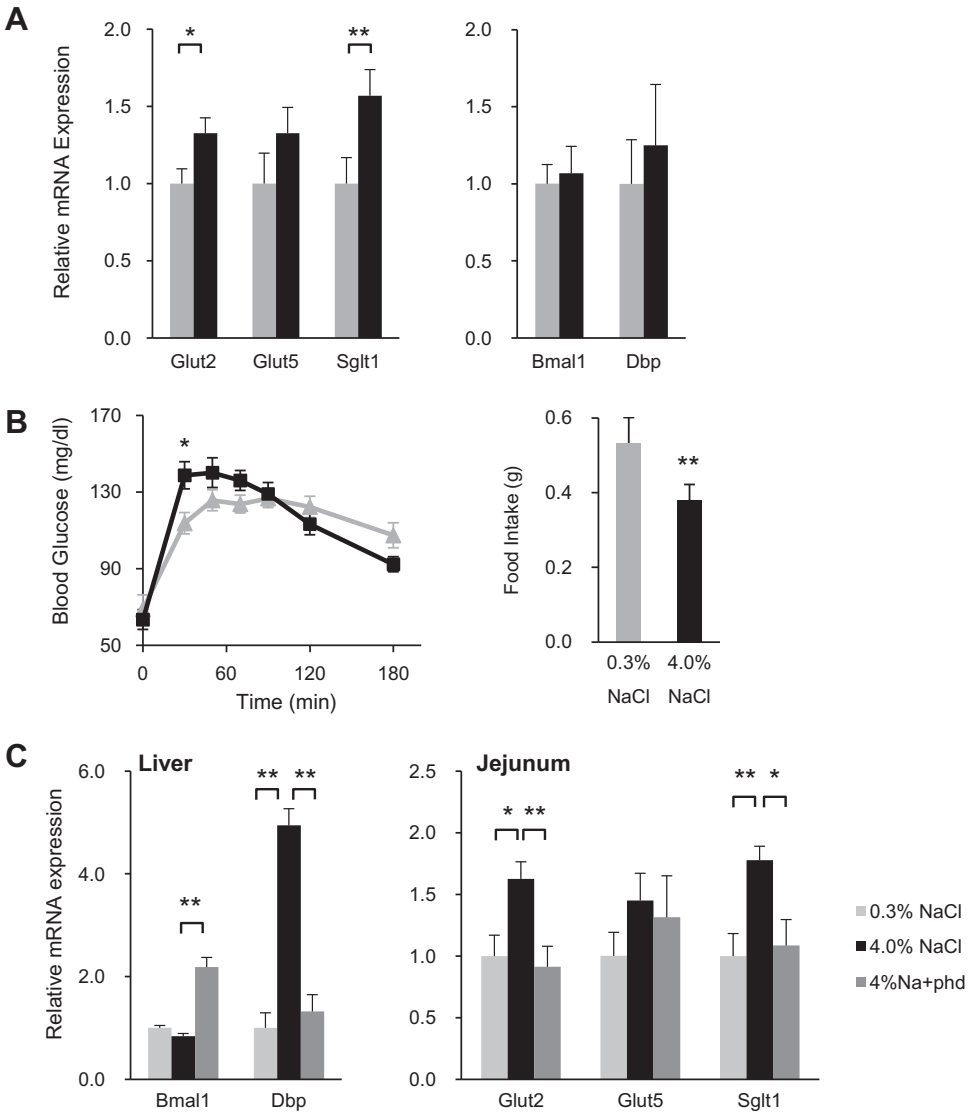

Fig. 4. High-salt diet alters glucose transport in jejunum. (A) Transcripts of glucose transporters (*Glut2*, *Glut5*, and *Sglt1*; left panel) and clock genes (*Bmal1* and *Dbp*; right panel) at ZT5 in jejunum of mice fed with NS (gray bars) and HS (black bars) diets for 1 week measured by quantitative RT-PCR ($n = 13$). (B) Blood glucose level (left panel) and dietary intake (right panel) after being fed NS (gray, $n = 13$) or HS (black, $n = 14$) diets for 30 min. (C) Transcripts of clock genes (*Bmal1* and *Dbp*; left panel) in liver and glucose transporters (*Glut2*, *Glut5*, and *Sglt1*; right panel) in jejunum of mice fed with NS (light gray bars), HS (black bars) and HS diet with 1% phloridzin (dark gray bars), an inhibitor of SGLT1, for 2 weeks measured by quantitative RT-PCR ($n = 6$). All data are presented as means ± SEM. Significant differences are indicated as $^{*}p < 0.05$ and $^{**}p < 0.01$.

and *Dbp* expression in the jejunum was unaltered by week 1, suggesting that the peripheral clock had not advanced by the end of the first week on the HS diet, an effect that was also evident in the liver, kidneys, and lungs (Fig. 1). We then measured blood glucose levels immediately after feeding according to the following schedule: NS or HS diet for 1 week, fasting for 1 day, re-feeding for 30 min. Blood glucose uptake was significantly acute in mice given the HS diet, although these mice consumed significantly less food than those given the NS diet (Fig. 4B).

Finally, to determine whether the increased glucose transport is associated with phase advancement caused by the HS diet, mice on this diet were also treated with or without phloridzin, a specific SGLT1 inhibitor. Oral phloridzin administered with food reduces blood glucose levels and decreases *Sglt1* expression in diabetic model mice [14]. The expression of *Sglt1* and *Glut2* in the jejunum and *Dbp* in the liver was significantly increased by the end of week 2 on the control HS diet (Fig. 4C), indicating that the this diet increased glucose absorption in the jejunum and advanced the clock in the liver as shown in Figs. 1 and 4A. The addition of phloridzin to the HS diet obviously inhibited the induction of *Glut2* and *Sglt1* expression in jejunum, decreased *Dbp* and increased *Bmal1* in the liver, suggesting that phase advancement was also suppressed.

4. Discussion

We show here that consumption of an HS diet caused phase advancement of circadian gene expression in peripheral tissues. The effect of the HS diet on phase advancement is conspicuous for the genes with peak expression during the dark phase relative to feeding time. This result suggests that dietary high salt affects the food entrainment of peripheral clocks at feeding time. We suggest that functional SGLT1 induction by an HS diet gradually causes phase advancement in peripheral clocks via increased glucose absorption in the jejunum, while functional inhibition of SGLT1 by phloridzin prevents this phase advancement via suppressing glucose transporter expression.

Short-term consumption of dietary HS does not cause hypertension in normal mouse and rat strains [15,16], although long-term consumption of 4% or 8% NaCl in the diet is a popular method of inducing hypertension in salt-sensitive Dahl rats [17]. A few reports have shown that the short-term administration of a diet containing 4% salt alters physiology and transcription. The present findings demonstrate that dietary salt alters glucose transport in the mouse intestine, and that this alteration affects circadian clock entrainment by food.

Notably the phase advancement of gene expression in peripheral tissues induced by dietary HS was not due to a change in feeding timing or the volume of food intake. Alterations in glucose absorption might be critical for phase advancement caused by a diet that is high in salt because intestinal absorption of nutrients is necessary to maintain specific peripheral rhythms such as that of blood corticosterone [9]. Intestinal glucose transporters are responsible for transporting sugars from the intestinal lumen to the blood. SGLT1 and GLUT5 are located in the apical membrane, where they transport monosaccharides from the intestinal lumen into the cytosol, while GLUT2 is basolaterally localized and transports sugars from the cytosol into the blood. These transporters are regulated by diet; a low-salt diet decreases *Sglt1* in chickens, and a high-fructose diet increases *Glut5* expression in mice [8]. Our observation that an HS diet induced the expression of *Sglt1*, but not of *Glut5*, seems to implicate sodium as the driving force behind glucose transport by *Sglt1*, but not by *Glut5*. Functional inhibition of SGLT1 by phloridzin prevented the induction of *Sglt1*, a result similar to that identified in streptozotocin-induced diabetic model mice [14], suggesting that glucose transport activity itself controls *Sglt1* expression by means of a feedback system.

Glucose is a most important nutrient and it can entrain the cellular clock in cultured fibroblasts [18]. A recent study has shown that feeding a combination of glucose with casein efficiently entrains the liver clock in mice [19], and the process of entrainment coincides with blood sugar uptake after feeding, suggesting that either blood glucose or its metabolites is a crucial factor for food entrainment of peripheral clocks. Coincidently, model animals with diabetes induced by streptozotocin have high blood glucose and peripheral clock advancement [20]. Moreover, *Sglt1* and *Glut2* expression and thus glucose absorption are increased in the small intestine of diabetic model animals [21]. The upregulation of glucose absorption by dietary HS might mimic food entrainment, resulting in the phase advancement of peripheral clocks. Notably, the time course of the HS dietary effect on phase advancement was tissue-dependent in this study and similar to food-induced phase resetting, which proceeds faster in the liver and kidneys than in the lungs [4,5].

The HS diet affected rhythmic gene expression, but the degree of phase advancement differed between groups. The effect was more powerful in the Cry1/Bmal1 and Per2 groups, which peaked during the dark period, compared with the Rora and Dbp/Per1 groups, which peaked during the light period, suggesting that nutritional signals affect the components of the dark period on the clock circuit. The coordinator of the cellular clock and energy metabolism, REV-ERBα, [22], might increase the transcription of genes during the feeding period in the Cry1/Bmal1 group, some of which have Rev-responsive elements (RRE). An unknown pathway might transmit nutritional signals for the transcription of genes in the Per2 group, because re-feeding of mice after fasting transiently increases *Per2* mRNA despite the mid-light period [23,24].

Almost all peripheral and some brain clocks including the food-entrainable oscillator, are entrained by food, indicating that they sense nutritional signals as a dominant zeitgeber. Nutritional content also considerably influences entrainment as we showed here.

Acknowledgments

This work was supported by "KAKENHI (20880036 and 21700778)" to H.O. and "The Salt Science Research Foundation, No. 0843." to H.O. and M.K. participated in study design, analytic supervision, data interpretation, and manuscript preparation. K.N., T.F., and N.I. participated in data analysis and data interpretation.

The authors thank Yokogawa Electric Co. for the loan of the DNA microarray reader and technical advice, and Mr. D. Uchida and Mr. R. Doi (University of Tsukuba) for helpful discussions.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bbrc.2010.09.072.

References

[1] S. Reppert, D. Weaver, Coordination of circadian timing in mammals, Nature 418 (2002) 935–941.
[2] J. Mendoza, Circadian clocks: setting time by food, J. Neuroendocrinol. 19 (2007) 127–137.
[3] C.B. Green, J.S. Takahashi, J. Bass, The meter of metabolism, Cell 134 (2008) 728–742.
[4] K. Stokkan, S. Yamazaki, H. Tei, Y. Sakaki, M. Menaker, Entrainment of the circadian clock in the liver by feeding, Science 291 (2001) 490–493.
[5] F. Damiola, N. Le Minh, N. Preitner, B. Kornmann, F. Fleury-Olela, U. Schibler, Restricted feeding uncouples circadian oscillators in peripheral tissues from the central pacemaker in the suprachiasmatic nucleus, Genes Dev. 14 (2000) 2950–2961.
[6] 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.
[7] K. Oishi, D. Uchida, N. Ohkura, R. Doi, N. Ishida, K. Kadota, S. Horie, Ketogenic diet disrupts the circadian clock and increases hypofibrinolytic risk by inducing expression of plasminogen activator inhibitor-1, Arterioscler. Thromb. Vasc. Biol. 29 (2009) 1571–1577.
[8] R.P. Ferraris, Dietary and developmental regulation of intestinal sugar transport, Biochem. J. 360 (2001) 265–276.
[9] H. Kato, M. Saito, T. Shimazu, Attenuated blood corticosterone rhythm in rats with jejunal resection, Life Sci. 34 (1984) 331–335.
[10] K. Nagai, Y. Takahashi, I. Mikami, T. Fukusima, H. Oike, M. Kobori, The hydroxyflavone, fisetin, suppresses mast cell activation induced by interaction with activated T cell membranes, Br. J. Pharmacol. 158 (2009) 907–919.
[11] N. Ohkura, K. Oishi, T. Sakata, K. Kadota, M. Kasamatsu, N. Fukushima, A. Kurata, Y. Tamai, H. Shirai, G. Atsumi, N. Ishida, J. Matsuda, S. Horie, Circadian variations in coagulation and fibrinolytic factors among four different strains of mice, Chronobiol. Int. 24 (2007) 651–669.
[12] X. Yang, M. Downes, R.T. Yu, A.L. Bookout, W. He, M. Straume, D.J. Mangelsdorf, R.M. Evans, Nuclear receptor expression links the circadian clock to metabolism, Cell 126 (2006) 801–810.
[13] S. Panda, M.P. Antoch, B.H. Miller, A.I. Su, A.B. Schook, M. Straume, P.G. Schultz, S.A. Kay, J.S. Takahashi, J.B. Hogenesch, Coordinated transcription of key pathways in the mouse by the circadian clock, Cell 109 (2002) 307–320.
[14] S. Masumoto, Y. Akimoto, H. Oike, M. Kobori, Dietary phloridzin reduces blood glucose levels and reverses Sglt1 expression in the small intestine in streptozotocin-induced diabetic mice, J. Agric. Food Chem. 57 (2009) 4651–4656.
[15] M.E. Alfie, D.H. Sigmon, S.I. Pomposiello, O.A. Carretero, Effect of high salt intake in mutant mice lacking bradykinin-B2 receptors, Hypertension 29 (1997) 483–487.
[16] J.W. Gu, A.P. Bailey, W. Tan, M. Shparago, E. Young, Long-term high salt diet causes hypertension and decreases renal expression of vascular endothelial growth factor in Sprague–Dawley rats, J. Am. Soc. Hypertens. 2 (2008) 275–285.
[17] L.K. Dahl, M. Heine, L. Tassinari, Effects of chronia excess salt ingestion. Evidence that genetic factors play an important role in susceptibility to experimental hypertension, J. Exp. Med. 115 (1962) 1173–1190.
[18] T. Hirota, T. Okano, K. Kokame, H. Shirotani-Ikejima, T. Miyata, Y. Fukada, Glucose down-regulates Per1 and Per2 mRNA levels and induces circadian gene expression in cultured Rat-1 fibroblasts, J. Biol. Chem. 277 (2002) 44244–44251.
[19] A. Hirao, Y. Tahara, I. Kimura, S. Shibata, A balanced diet is necessary for proper entrainment signals of the mouse liver clock, PLoS One 4 (2009) e6909.
[20] K. Oishi, M. Kasamatsu, N. Ishida, Gene- and tissue-specific alterations of circadian clock gene expression in streptozotocin-induced diabetic mice under restricted feeding, Biochem. Biophys. Res. Commun. 317 (2004) 330–334.

[21] J. Dyer, I.S. Wood, A. Palejwala, A. Ellis, S.P. Shirazi-Beechey, Expression of monosaccharide transporters in intestine of diabetic humans, Am. J. Physiol. Gastrointest. Liver Physiol. 282 (2002) G241–G248.
[22] L. Yin, N. Wu, J.C. Curtin, M. Qatanani, N.R. Szwergold, R.A. Reid, G.M. Waitt, D.J. Parks, K.H. Pearce, G.B. Wisely, M.A. Lazar, Rev-erbalpha, a heme sensor that coordinates metabolic and circadian pathways, Science 318 (2007) 1786–1789.
[23] H. Kobayashi, K. Oishi, S. Hanai, N. Ishida, Effect of feeding on peripheral circadian rhythms and behaviour in mammals, Genes Cells 9 (2004) 857–864.
[24] T. Wu, Y. Ni, H. Kato, Z. Fu, Feeding-induced rapid resetting of the hepatic circadian clock is associated with acute induction of Per2 and Dec1 transcription in rats, Chronobiol. Int. 27 (2010) 1–18.