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Circadian rhythm of intracellular protein synthesis signaling in rat cardiac and skeletal muscles

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ABSTRACT

Intracellular signaling exhibits circadian variation in the suprachiasmatic nucleus and liver. However, it is unclear whether circadian regulation also extends to intracellular signaling pathways in the cardiac and skeletal muscles. Here, we examined circadian variation in the intracellular mammalian target of rapamycin (mTOR)/70 kDa ribosomal protein S6 kinase 1 (p70S6K) and extracellular signal-regulated kinase (ERK) pathways, which regulate protein synthesis in rat cardiac and skeletal muscles. Seven-week-old male Wistar rats were assigned to six groups: Zeitgeber time (ZT) 2, ZT6, ZT10, ZT14, ZT18, and ZT22 (ZT0, lights on; ZT12, lights off). The cardiac, plantaris, and soleus muscles were removed after a 12-h fasting period, and signal transducers involved in protein synthesis (mTOR, p70S6K, and ERK) were analyzed by western blotting. Circadian rhythms of signal transducers were observed in both cardiac (mTOR, p70S6K, and ERK) and plantaris (p70S6K and ERK) muscles ($p < 0.05$), but not in the soleus muscle. In the cardiac muscle, the phosphorylation rate of mTOR was significantly higher at ZT6 (peak) than at ZT18 (bottom), and the phosphorylation rate of p70S6K was significantly higher at ZT2 (peak) than at ZT18 (bottom). In contrast, in the plantaris muscle, the phosphorylation rate of ERK was significantly lower at ZT2 (bottom) than at ZT18 (peak). Our data suggested that protein synthesis via mTOR/p70S6K and ERK signaling molecules exhibits circadian variation in rat cardiac and fast-type plantaris muscles.

1. Introduction

Various physiological and metabolic processes, such as behavioral patterns, heart rate, blood pressure, and hormone secretion, exhibit a 24 h rhythm. These circadian rhythms are regulated by the central circadian clock, which is present in the suprachiasmatic nucleus (SCN) of the hypothalamus. The SCN (central clock) plays a key role in the regulation of homeostatic functions and mediates the entrainment of the circadian rhythm to the environmental light/dark cycle [1].

Recent reports have demonstrated that the clock machinery is expressed not only in the SCN, but also in almost all other tissues, such as the heart, liver, kidney, and skeletal muscle [2,3]. Moreover, the peripheral clocks regulate diurnal changes in tissue-specific physiological processes. Numerous studies have indicated that clock genes, such as *CLOCK* and *BMAL1*, regulate the circadian rhythm in peripheral tissues [4,5]. The loss of these clock genes influences the function and growth of the liver, cardiac, and skeletal muscles of mice [3,6,7]. Additionally, more recent studies in mice have shown that the phosphorylation of molecules in intracellular signaling pathways, such as the extracellular signal-regulated kinase (ERK) and S6 ribosomal protein (rpS6) pathways, exhibits a circadian rhythm in the SCN [8,9] and regulates the output and input of the circadian clock. In the SCN, the ERK signaling pathway plays an important role in the clock-resetting mechanisms of mammalian circadian rhythms [10,11]. Moreover, rpS6 phosphorylation is regulated by the activation of mammalian target of rapamycin (mTOR) and its downstream target 70 kDa ribosomal protein S6 kinase 1 (p70S6K); the activation of this pathway leads to mRNA translation and protein synthesis [12]. However, it is not clear whether the phosphorylation of these pathways regulates the function of the circadian clock in peripheral tissues.

Interestingly, a recent report demonstrated that ERK signaling strictly regulates the circadian clock in mouse peripheral liver tissue, suggesting that the circadian oscillation of ERK activity regulates diurnal variation in liver function and homeostasis [13]. Furthermore, Lipton et al. [14] demonstrated that expression of the core clock protein BMAL1 in the mouse liver is mediated by the phosphorylation of mTOR/p70S6K and controls circadian timing. These pathways also play important roles in muscle growth and hypertrophy in the cardiac and skeletal muscles [15–17]; therefore, the circadian rhythm of these signaling pathways may be associated

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with dairy muscle protein turnover and muscle adaptation. However, circadian regulation of mTOR/p70S6K and ERK pathways in other peripheral tissues, such as the cardiac and skeletal muscles, is not well understood.

Therefore, in this study, we aimed to determine whether the activation of protein synthesis-related intracellular signaling pathways, such as the mTOR/p70S6K and ERK pathways, is involved in circadian rhythms in rat cardiac and skeletal muscles.

2. Materials and methods

2.1. Experimental animals and experimental design

The experiments in this study were approved by the Juntendo University Animal Care and Use Committee. Seven-week-old male Wistar rats were obtained from a licensed laboratory animal vendor (SLC Inc., Hamamatsu, Shizuoka, Japan). Rats were housed in an environmentally controlled room (temperature: 23 ± 1 °C; humidity: 55% ± 5%; 12 h dark/light cycle, with lights on at 18:00 and lights off at 6:00). Water and food were provided *ad libitum*.

Rats (n=48) were acclimated for 2 weeks and were then assigned to six Zeitgeber time points (ZT0, lights on at 18:00; ZT12, lights off at 6:00): ZT2 (n=8), ZT6 (n=8), ZT10 (n=8), ZT14 (n=8), ZT18 (n=8), and ZT22 (n=8). After 12 h of fasting, the rats were anesthetized with pentobarbital sodium (50 mg/kg) at each time point (ZT2, ZT6, ZT10, ZT14, ZT18, and ZT22), and blood samples were collected from an abdominal vein. Cardiac, plantaris, and soleus muscles were quickly removed, weighed, and frozen in liquid nitrogen. Samples were stored at −80 °C until analysis.

Preparation of blood, cardiac muscle, and skeletal muscle samples.

Blood samples were centrifuged at 3000 rpm for 10 min to obtain serum and stored at −80 °C. Growth hormone (GH) and corticosterone concentrations were estimated by commercial laboratories (Shibayagi Co., Ltd., Shibukawa, Japan and Oriental Yeast Co., Ltd., Tokyo, Japan).

For protein analyses, the cardiac and plantaris muscles were powdered in liquid nitrogen. Samples were then homogenized in ice-cold homogenization buffer (50 mM HEPES [pH 7.4], 1 mM EDTA, 1 mM EGTA, 20 mM β-glycerophosphate, 1 mM Na_3VO_4, 10 mM NaF, 1% Triton X-100) containing a protease inhibitor cocktail (Complete EDTA-free; Roche, Penzberg, Germany) and phosphatase inhibitor cocktail (PhosSTOP; Roche). Homogenates were centrifuged at 12,000×*g* for 15 min at 4 °C, and the protein concentrations of the supernatants were determined using a BCA Protein Assay Kit (Thermo, Rockford, IL, USA).

2.2. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), western blotting, and immunodetection

To determine the protein expression and phosphorylation status in the muscles, SDS-PAGE and immunodetection were performed using techniques previously described by Yoshihara et al. [18]. Briefly, protein extracts were solubilized in sample buffer [99% glycerol, 2-β-mercaptoethanol, 20% SDS, 1 M Tris-HCl (pH 6.8), and bromophenol blue] and incubated at 95 °C for 5 min. Equal amounts of protein were then loaded onto 10% TGX FastCast acrylamide gels (Bio-Rad Laboratories, Hercules, CA, USA) and run at 150 V for 50 min. Separated proteins were transferred to PVDF membranes (Bio-Rad Laboratories) using a Bio-Rad Mini Trans-Blot cell at 100 V for 60 min at 4 °C in transfer buffer (25 mM Tris, 192 mM glycine, and 20% methanol). After transfer, membranes were blocked for 1 h using blocking buffer (5% nonfat dry milk in Tween-Tris-buffered saline [T-TBS: 40 mM Tris-HCl, 300 mM NaCl, and 0.1% Tween 20, pH7.5]) at room temperature. The membranes were then incubated with the following primary antibodies: anti-phospho-mTOR Ser2448 (1:2000; #2971; Cell Signaling Technology, Danvers, MA, USA), anti-mTOR (1:2000; #2972; Cell Signaling Technology), anti-phospho-p70S6K Thr389 (1:2000; #9234; Cell Signaling Technology), anti-p70S6K (1:2000; #9202; Cell Signaling Technology), anti-phospho-p44/42 ERK1/2 Thr202/Thr204 (1:5000; #4370; Cell Signaling Technology), and anti-p44/42 ERK1/2 (1:5000; #4695; Cell Signaling Technology) in dilution buffer for 2 h at room temperature. After several washes in T-TBS, membranes were incubated with anti-rabbit horseradish peroxidase (HRP)-conjugated secondary antibodies (1:5000; #7074; Cell Signaling Technology) in dilution buffer for 1 h at room temperature. After several washes in T-TBS, proteins were visualized using Immobilon Western Chemiluminescent HRP Substrate (Millipore Corporation, Billerica, MA, USA), and signals were recorded using an ATTO Light Capture System (Tokyo, Japan). Analyses were performed using CS ANALYZER 3.0 (ATTO, Amherst, NY, USA). The ratio of phosphorylated protein to total protein expression was determined using arbitrary units.

2.3. Statistical analysis

All values are presented as means ± standard errors (SEs). Boxplots were used to identify outliers (Q1−(1.5×IQR) or Q3+(1.5×IQR)) in the data set. Circadian rhythms were analyzed statistically using the modified cosinor analysis (nonlinear least-squares [NLLS] Marquardt–Levenberg algorithm) [19]. The function was defined as $f(x)=M+A\times\cos(2p/T[x-ø])$, where M is the mesor (the average cycle value), A represents the amplitude (half the distance between peaks of the fitted waveform), T represents the circadian period, and ø is the acrophase (time point in the cycle of highest amplitude in radians). The circadian period (T) was 24 h under 12 h light and 12 h dark periods. Acrophase is expressed as hours elapsed from ZT0. The significance of circadian rhythmicity was assessed using the zero-amplitude test; *p*-values of less than 0.05 were considered statistically significant for the given period of the cosine curve approximation. Differences among groups were analyzed using a one-way analysis of variance (ANOVA). When a significant difference was observed, a post-hoc Scheffe's test was performed. Differences with *p*-values of less than 0.05 were considered statistically significant. All statistical analyses were performed using SPSS v. 22.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Signal transduction

Fig. 1 shows the circadian variation in the mTOR, p70S6K, and ERK1/2 phosphorylation rate in the cardiac (A, B, and C), plantaris (D, E, and F), and soleus (G, H, and I) muscles. The total protein expression levels of mTOR, p70S6K, and ERK1/2 did not differ significantly among the experimental groups in the cardiac, plantaris, and soleus muscles (data not shown).

The cosinor analysis indicated that the rates of mTOR, p70S6K, and ERK1/2 phosphorylation displayed robust circadian rhythms in the cardiac muscle. The rate of mTOR phosphorylation was higher at ZT2 than at ZT18 ($p < 0.01$, bottom). The phosphorylation rate at ZT6 (peak) was significantly higher than those at ZT14 ($p < 0.01$), ZT18 ($p < 0.001$, bottom), and ZT22 ($p < 0.01$). Moreover, the phosphorylation rate of p70S6K at ZT2 (peak) was significantly elevated compared with those at ZT14 ($p < 0.01$) and ZT18 ($p < 0.01$, bottom). The phosphorylation rate at ZT6 was significantly higher than that at ZT18 ($p < 0.05$, bottom) in the cardiac muscle. No significant differences were observed among time points in the phosphorylation rate of ERK1/2 in the cardiac muscle.

In the plantaris muscle, a cosinor analysis confirmed circadian rhythms in the phosphorylation rates of p70S6K and ERK1/2. There were no significant differences in the phosphorylation rates of mTOR and p70S6K among time points. However, the ERK1/2 phosphorylation rate was significantly lower at ZT2 ($p < 0.001$, bottom), ZT6 ($p <$

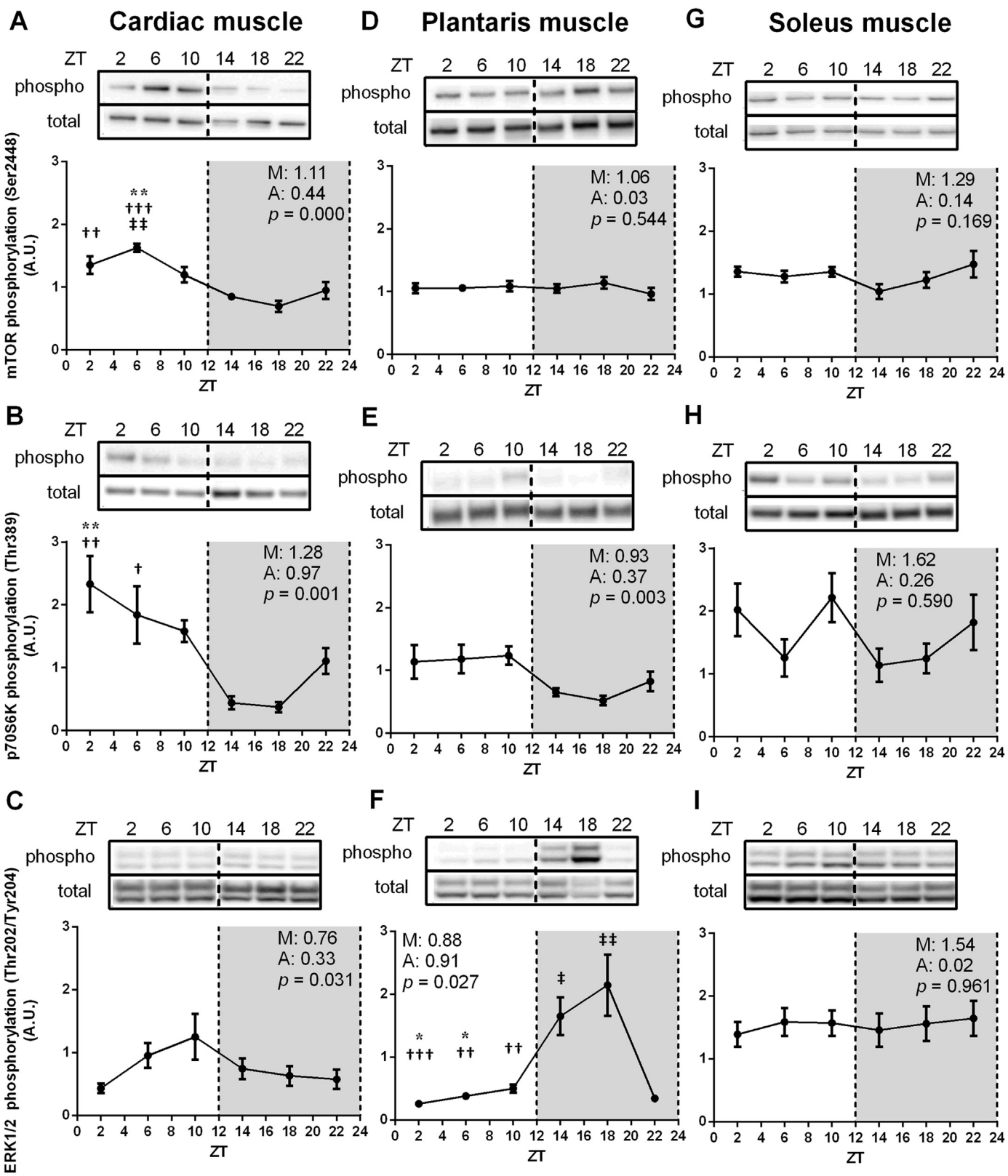

Fig. 1. mTOR (A, D, and G), p70S6K (B, E, and H), and ERK1/2 (C, F, and I) phosphorylation rates in the cardiac (left), plantaris (median), and soleus (right) muscles over 24 h. Gray shading indicates the dark period. Samples were collected at Zeitgeber times (ZT) 2, ZT6, ZT10, ZT14, ZT18, and ZT22 after 12 h of fasting. Values are presented as means ± standard errors (SEs). $^{**}p < 0.01$, $^{*}p < 0.05$ versus ZT14; $^{\dagger\dagger\dagger}p < 0.001$, $^{\dagger\dagger}p < 0.01$, $^{\dagger}p < 0.05$ versus ZT18; $^{\ddagger\ddagger}p < 0.01$, $^{\ddagger}p < 0.05$ versus ZT22. MESOR (M), the average cycle value; amplitude (A), half the distance between peaks of the fitted waveform; p values were obtained from cosinor analysis. n=6–8.

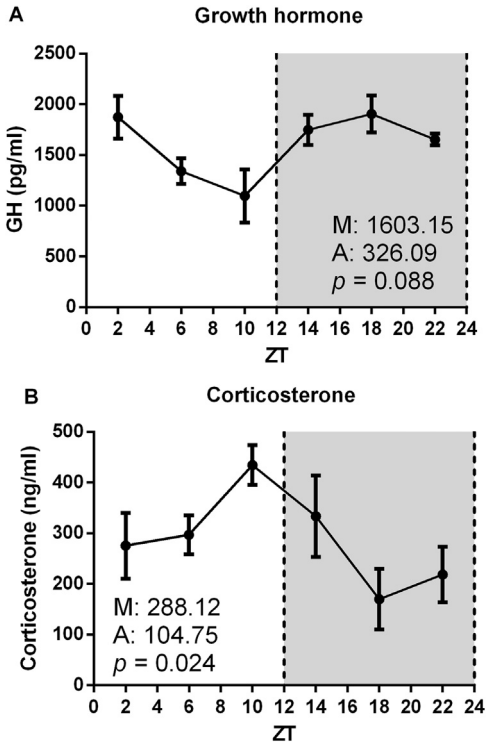

Fig. 2. Serum growth hormone levels (A) and serum corticosterone levels (B) over 24 h. Samples were collected at ZT2, ZT6, ZT10, ZT14, ZT18, and ZT22 after 12 h of fasting. Values are presented as means ± SEs. The *p*-values were obtained from a cosinor analysis. n=6.

0.01), and ZT10 ($p < 0.01$) than at ZT18 (peak). The phosphorylation rates at ZT2 ($p < 0.05$, bottom) and ZT6 ($p < 0.05$) were significantly lower than that at ZT14, and the phosphorylation rates at ZT14 ($p < 0.05$) and ZT18 ($p < 0.01$, peak) were significantly higher than that at ZT22.

In contrast, circadian rhythms were not confirmed in the soleus muscle and there were no significant differences in the phosphorylation rates of mTOR, p70S6K, and ERK1/2 among time points.

3.2. Growth hormone and corticosterone levels

Fig. 2 shows the circadian variation in serum growth hormone and corticosterone levels. The cosinor analysis indicated that serum corticosterone levels displayed robust circadian rhythms, but not serum growth hormone levels. No significant differences in serum growth hormone and corticosterone levels were observed among time points.

4. Discussion

We examined whether the activation of intracellular signaling pathways, such as muscle protein synthesis-related mTOR/p70S6K and ERK signaling pathways, exhibited circadian rhythms in rat cardiac and skeletal muscles. Although the underlying mechanisms by which intracellular signaling exhibits circadian variation are still unclear, our results demonstrated, for the first time, the occurrence of circadian oscillations in the phosphorylation of mTOR/p70S6K and ERK pathway components in cardiac and fast-type plantaris muscles.

One of our main findings was mTOR/p70S6K signaling exhibited circadian variation in the cardiac muscle. mTOR and its key downstream target p70S6K have important roles in the determination of cardiac cell size and contractile function [20,21]. Our data indicated that circadian oscillation of the phosphorylation of mTOR/p70S6K may regulate variation in cardiac muscle function and homeostasis. Although little is known about the mechanisms underlying circadian oscillation in mTOR/p70S6K signaling in the cardiac muscle, mTOR/p70S6K signaling is important for cell growth and is activated by multiple extracellular signals, such as growth factors and nutritional, chemical, and mechanical stimuli [22]. GH is a growth factor that increases insulin and insulin-like growth factor (IGF)−1 transport to tissues. Given that insulin and IGF-1 activate mTOR signaling, the circadian oscillation in GH levels may affect the phosphorylation of mTOR and its downstream transducers. However, in the present study, no significant circadian changes were observed in serum GH levels, this observation is in agreement with previous studies [23]. This may be because we performed experiments after 12 h of fasting in order to remove the effects of factors related to mTOR signaling activation, such as nutritional stimuli. Previous reports have indicated that long-term food restriction (fasting for more than 24 h) can have many physiological effects, e.g., low body temperature, high eosinophil counts, high corticosterone levels, and low p70S6K phosphorylation [24–26]; however, short-term food restriction (fasting for less than 24 h) has a relatively minor effect [24,27]. Furthermore, previous reports have indicated that food restriction causes a time-dependent inactivation of mTOR/p70S6K [28,29], whereby the inactivation of mTOR/p70S6K becomes progressively greater as food deprivation continues. In our study, 12 h of fasting may have minimal effects on the circadian rhythm waveform of mTOR/p70S6K phosphorylation. However, mTOR/p70S6K signaling in the cardiac muscle is activated mainly by cardiac work and physical activity [30]. Restricted feeding can reduce behavioral activity and result in similar heart rates during light and dark periods [31]. Therefore, in the present study, the contributions of GH, physical activity, and heart rate to circadian changes in mTOR/p70S6K phosphorylation may be minimal. Importantly, our data revealed that serum corticosterone exhibits a circadian rhythm, with peaks at ZT10–ZT12, in agreement with previous experiments [19,26].

Circadian rhythms of circulating corticosterone are controlled by the hypothalamic-pituitary-adrenal axis in the SCN. Galicich et al. reported that circadian desynchronization of adrenocorticotropic hormone (ACTH, which stimulates the secretion of corticosterone) results from suprapontine brain ablation in mice [32]. Therefore, the central nervous system is closely related to corticosterone fluctuations. Shah et al. demonstrated that the phosphorylation of p70S6K is suppressed by a glucocorticoid concentration that is equivalent to corticosterone in rats and cortisol in humans [33]. Furthermore, recent reports have demonstrated that *BMAL1* is regulated by corticosterone [34,35]. *BMAL1* is mediated by the phosphorylation of mTOR/p70S6K and has crucial roles in the control of circadian timing [14]. Therefore, circadian variation in serum corticosterone levels may regulate mTOR/p70S6K signaling variation in the cardiac muscle.

p70S6K phosphorylation in the plantaris and cardiac muscles varied with changes in corticosterone levels; however, mTOR phosphorylation was unchanged. In the skeletal muscle, mTOR senses multiple extracellular signals, such as nutritional, chemical, and mechanical stimuli; therefore, mTOR phosphorylation at Ser2448 does not always indicate its activation. Given that numerous previous studies have used p70S6K phosphorylation at Thr389 as a functional indicator of mTOR activity [18,36], mTOR phosphorylation at Ser2448 in the plantaris muscle may not exhibit a circadian rhythm under our experimental conditions.

Our data also revealed that ERK signaling phosphorylation exhibited circadian variation in both cardiac and plantaris muscles. The circadian oscillation of ERK expression has been reported in the mouse SCN, in which ERK expression peaked in the inactive phase (light stage) and reached a minimum in the active phase (dark stage) [37]. The same results were observed in the cardiac muscle in the current study. In contrast, in the plantaris muscle, the phosphorylation rate of ERK peaked in the active (dark) phase and remained low in the inactive (light) phase. This may reflect differences in physiological roles of ERK between the SCN and skeletal muscle. In the SCN, the ERK pathway is involved in photic entrainment, regulates phase shifting of behavioral

rhythms, and is activated by light [8]. In contrast, ERK signaling plays a role in the signaling network required for regeneration and hypertrophy [38] and is activated by exercise [39], GH [40], and corticosterone [41] in the skeletal muscle. The circadian rhythm waveform of ERK phosphorylation in the cardiac muscle showed the opposite trend in the plantaris muscle, suggesting that ERK phosphorylation had different effects in different organs. However, the physiological significance of circadian variation in ERK phosphorylation in the cardiac and plantaris muscles remains unclear.

Interestingly, p70S6K and ERK phosphorylation exhibited circadian variation in the fast-type plantaris muscle, but not in the slow-type soleus muscle in the current study. Unfortunately, the specific mechanisms underlying the muscle type-specific differences in the phosphorylation of signaling molecules in the plantaris and soleus muscles are currently unknown. Nonetheless, these differences could be associated with the observation that slow-type muscles have a higher frequency of activity in daily life than fast-type muscles. Slow-type muscles are primarily thought to maintain posture and are used in daily activity [42]. In contrast, fast-type muscle can generate the more force and, in particular, the force necessary for specific activities. Additionally, fast-type muscles are more susceptible to changes in nutrients and hormones than slow-type muscles [41,43]. p70S6K and ERK phosphorylation exhibit fiber-type specific responses to insulin and isoproterenol in the skeletal muscle (greater than that in slow-type muscles) [44,45]. These differences may be related to the observation that slow-type muscles have a higher protein turnover rate than fast-type muscles [46,47]. Nonetheless, given that the phosphorylation of these signaling proteins may be regulated by the corticosterone concentration, as demonstrated in the present study, it appears likely that circadian variation in intracellular signaling transduction in the slow-type muscles is minor. Further research is required to determine the mechanisms underlying type-specific circadian rhythms in the phosphorylation of signal transducers.

In summary, our data demonstrated that circadian oscillations occur in the phosphorylation of the mTOR/p70S6K and ERK pathways in the cardiac and plantaris muscles and that this variation is dependent on muscle type. Although the specific mechanisms responsible for the phosphorylation of these signaling pathway components remain unclear, the components may be partially regulated by the corticosterone concentration, suggesting that the circadian oscillation in the activities of protein synthesis-related intracellular signaling pathways regulate circadian variation in various tissue-specific functions and homeostasis. Further studies are required to clarify the relevance of circadian rhythms in the phosphorylation of signaling pathway components and the mechanisms underlying circadian changes in the mTOR/p70S6K and ERK signaling pathways in muscles.

5. Conflict of interest

No conflicts of interest, financial or otherwise, are declared by the authors.

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Appendix A. Transparency document

Transparency data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.bbrep.2016.12.005.

References

[1] K.P. Wright, A.W. McHill, B.R. Birks, B.R. Griffin, T. Rusterholz, E.D. Chinoy, Entrainment of the human circadian clock to the natural light-dark cycle, Curr. Biol. 23 (2013) 1554–1558.
[2] J. Richards, M.L. Gumz, Mechanism of the circadian clock in physiology, Am. J. Physiol.-Regul. Integr. Comp. Physiol. 304 (2013) R1053–R1064.
[3] J.L. Andrews, X. Zhang, J.J. McCarthy, E.L. McDearmon, T.A. Hornberger, B. Russell, K.S. Campbell, S. Arbogast, M.B. Reid, J.R. Walker, CLOCK and BMAL1 regulate MyoD and are necessary for maintenance of skeletal muscle phenotype and function, Proc. Natl. Acad. Sci. USA 107 (2010) 19090–19095.
[4] J.J. McCarthy, J.L. Andrews, E.L. McDearmon, K.S. Campbell, B.K. Barber, B.H. Miller, J.R. Walker, J.B. Hogenesch, J.S. Takahashi, K.A. Esser, Identification of the circadian transcriptome in adult mouse skeletal muscle, Physiol. Genom. 31 (2007) 86–95.
[5] S.M. Reppert, D.R. Weaver, Coordination of circadian timing in mammals, Nature 418 (2002) 935–941.
[6] K.A. Lamia, K.-F. Storch, C.J. Weitz, Physiological significance of a peripheral tissue circadian clock, Proc. Natl. Acad. Sci. USA 105 (2008) 15172–15177.
[7] M.S. Bray, C.A. Shaw, M.W. Moore, R.A. Garcia, M.M. Zanquetta, D.J. Durgan, W.J. Jeong, J.-Y. Tsai, H. Bugger, D. Zhang, Disruption of the circadian clock within the cardiomyocyte influences myocardial contractile function, metabolism, and gene expression, Am. J. Physiol.-Heart Circ. Physiol. 294 (2008) H1036–H1047.
[8] A.N. Coogan, H.D. Piggins, MAP kinases in the mammalian circadian system–key regulators of clock function, J. Neurochem. 90 (2004) 769–775.
[9] R. Cao, F.E. Anderson, Y.-J. Jung, H. Dziema, K. Obrietan, Circadian regulation of mammalian target of rapamycin signaling in the mouse suprachiasmatic nucleus, Neuroscience 181 (2011) 79–88.
[10] K. Obrietan, S. Impey, D.R. Storm, Light and circadian rhythmicity regulate MAP kinase activation in the suprachiasmatic nuclei, Nat. Neurosci. 1 (1998) 693–700.
[11] M. Akashi, E. Nishida, Involvement of the MAP kinase cascade in resetting of the mammalian circadian clock, Genes Dev. 14 (2000) 645–649.
[12] I. Ruvinsky, O. Meyuhas, Ribosomal protein S6 phosphorylation: from protein synthesis to cell size, Trends Biochem. Sci. 31 (2006) 342–348.
[13] Y. Tsuchiya, I. Minami, H. Kadotani, T. Todo, E. Nishida, Circadian clock-controlled diurnal oscillation of Ras/ERK signaling in mouse liver, Proc. Jpn. Acad. Ser. B 89 (2013) 59–65.
[14] J.O. Lipton, E.D. Yuan, L.M. Boyle, D. Ebrahimi-Fakhari, E. Kwiatkowski, A. Nathan, T. Güttler, F. Davis, J.M. Asara, M. Sahin, The circadian protein BMAL1 regulates translation in response to S6K1-mediated phosphorylation, Cell 161 (2015) 1138–1151.
[15] A. Kenessey, K. Ojamaa, Thyroid hormone stimulates protein synthesis in the cardiomyocyte by activating the Akt-mTOR and p70S6K pathways, J. Biol. Chem. 281 (2006) 20666–20672.
[16] J.D. Parkington, N.K. LeBrasseur, A.P. Siebert, R.A. Fielding, Contraction-mediated mTOR, p70S6k, and ERK1/2 phosphorylation in aged skeletal muscle, J. Appl. Physiol. 97 (2004) 243–248.
[17] C.F. Bentzinger, K. Romanino, D. Cloëtta, S. Lin, J.B. Mascarenhas, F. Oliveri, J. Xia, E. Casanova, C.F. Costa, M. Brink, Skeletal muscle-specific ablation of raptor, but not of rictor, causes metabolic changes and results in muscle dystrophy, Cell Metab. 8 (2008) 411–424.
[18] T. Yoshihara, H. Naito, R. Kakigi, N. Ichinoseki-Sekine, Y. Ogura, T. Sugiura, S. Katamoto, Heat stress activates the Akt/mTOR signalling pathway in rat skeletal muscle, Acta Physiol. 207 (2013) 416–426.
[19] Y. Yasumoto, R. Nakao, K. Oishi, Free access to a running-wheel advances the phase of behavioral and physiological circadian rhythms and peripheral molecular clocks in mice, PloS One 10 (2015) e0116476.
[20] T. Shioi, J.R. McMullen, O. Tarnavski, K. Converso, M.C. Sherwood, W.J. Manning, S. Izumo, Rapamycin attenuates load-induced cardiac hypertrophy in mice, Circulation 107 (2003) 1664–1670.
[21] T. Ha, Y. Li, X. Gao, J.R. McMullen, T. Shioi, S. Izumo, J.L. Kelley, A. Zhao, G.E. Haddad, D.L. Williams, Attenuation of cardiac hypertrophy by inhibiting both mTOR and NFκB activation in vivo, Free Radic. Biol. Med. 39 (2005) 1570–1580.
[22] S. Sengupta, T.R. Peterson, D.M. Sabatini, Regulation of the mTOR complex 1 pathway by nutrients, growth factors, and stress, Mol. Cell 40 (2010) 310–322.
[23] A. Armario, J. Montero, T. Jolin, Chronic food restriction and the circadian rhythms of pituitary-adrenal hormones, growth hormone and thyroid-stimulating hormone, Ann. Nutr. Metab. 31 (1987) 81–87.
[24] T. Yoda, L.I. Crawshaw, K. Yoshida, L. Su, T. Hosono, O. Shido, S. Sakurada, Y. Fukuda, K. Kanosue, Effects of food deprivation on daily changes in body temperature and behavioral thermoregulation in rats, Am. J. Physiol.-Regul. Integr. Comp. Physiol. 278 (2000) R134–R139.
[25] F. Halberg, G. Cornélissen, G. Katinas, E.V. Syutkina, R.B. Sothern, R. Zaslavskaya, F. Halberg, Y. Watanabe, O. Schwartzkopff, K. Otsuka, Transdisciplinary unifying implications of circadian findings in the 1950s, J. Circadian Rhythms 1 (2003) 1.
[26] T. Shavlakadze, T. Anwari, Z. Soffe, G. Cozens, P.J. Mark, C. Gondro, M.D. Grounds, Impact of fasting on the rhythmic expression of myogenic and metabolic factors in skeletal muscle of adult mice, Am. J. Physiol.-Cell Physiol. 305 (2013) C26–C35.
[27] M.H. Nowland, K. Hugunin, K.L. Rogers, Effects of short-term fasting in male Sprague–Dawley rats, Comp. Med. 61 (2011) 138–144.
[28] T. Ogata, Y. Oishi, M. Higuchi, I. Muraoka, Fasting-related autophagic response in slow-and fast-twitch skeletal muscle, Biochem. Biophys. Res. Commun. 394 (2010) 136–140.

[29] T. Shavlakadze, Z. Soffe, T. Anwari, G. Cozens, M.D. Grounds, Short-term feed deprivation rapidly induces the protein degradation pathway in skeletal muscles of young mice, J. Nutr. 143 (2013) 403–409.
[30] O.J. Kemi, M. Ceci, U. Wisloff, S. Grimaldi, P. Gallo, G.L. Smith, G. Condorelli, O. Ellingsen, Activation or inactivation of cardiac Akt/mTOR signaling diverges physiological from pathological hypertrophy, J. Cell. Physiol. 214 (2008) 316–321.
[31] M. van den Buuse, Circadian rhythms of blood pressure and heart rate in conscious rats: effects of light cycle shift and timed feeding, Physiol. Behav. 68 (1999) 9–15.
[32] J. Galicich, F. Halberg, L. French, F. Ungar, Effect of cerebral ablation on a circadian pituitary adrenocorticotropic rhythm in C mice, Endocrinology 76 (1965) 895–901.
[33] O.J. Shah, S.R. Kimball, L.S. Jefferson, Glucocorticoids abate p70S6k and eIF4E function in L6 skeletal myoblasts, Am. J. Physiol.-Endocrinol. Metab. 279 (2000) E74–E82.
[34] R.R. Almon, E. Yang, W. Lai, I.P. Androulakis, S. Ghimbovschi, E.P. Hoffman, W.J. Jusko, D.C. DuBois, Relationships between circadian rhythms and modulation of gene expression by glucocorticoids in skeletal muscle, Am. J. Physiol.-Regul. Integr. Comp. Physiol. 295 (2008) R1031–R1047.
[35] Y. Dong, T. Wu, Y. Ni, H. Kato, Z. Fu, Effect of fasting on the peripheral circadian gene expression in rats, Biol. Rhythm Res. 41 (2010) 41–47.
[36] D.D. Sarbassov, S.M. Ali, D.M. Sabatini, Growing roles for the mTOR pathway, Curr. Opin. Cell Biol. 17 (2005) 596–603.
[37] A.N. Coogan, H.D. Piggins, Circadian and photic regulation of phosphorylation of ERK1/2 and Elk-1 in the suprachiasmatic nuclei of the Syrian hamster, J. Neurosci. 23 (2003) 3085–3093.
[38] N.C. Jones, Y.V. Fedorov, R.S. Rosenthal, B.B. Olwin, ERK1/2 is required for myoblast proliferation but is dispensable for muscle gene expression and cell fusion, J. Cell. Physiol. 186 (2001) 104–115.
[39] U. Widegren, C. Wretman, A. Lionikas, G. Hedin, J. Henriksson, Influence of exercise intensity on ERK/MAP kinase signalling in human skeletal muscle, Pflu¨g. Arch. 441 (2000) 317–322.
[40] A.A. Hayashi, C.G. Proud, The rapid activation of protein synthesis by growth hormone requires signaling through mTOR, Am. J. Physiol.-Endocrinol. Metab. 292 (2007) E1647–E1655.
[41] S. Boncompagni, L. Arthurton, E. Akujuru, T. Pearson, D. Steverding, F. Protasi, G. Mutungi, Membrane glucocorticoid receptors are localised in the extracellular matrix and signal through the MAPK pathway in mammalian skeletal muscle fibres, J. Physiol. 593 (2015) 2679–2692.
[42] A. Chopard, F. Pons, J.-F. Marini, Cytoskeletal protein contents before and after hindlimb suspension in a fast and slow rat skeletal muscle, Am. J. Physiol.-Regul. Integr. Comp. Physiol. 280 (2001) R323–R330.
[43] A. Baillie, P.J. Garlick, Responses of protein synthesis in different skeletal muscles to fasting and insulin in rats, Am. J. Physiol.-Endocrinol. Metab. 260 (1991) E891–E896.
[44] X.M. Song, J.W. Ryder, Y. Kawano, A.V. Chibalin, A. Krook, J.R. Zierath, Muscle fiber type specificity in insulin signal transduction, Am. J. Physiol.-Regul. Integr. Comp. Physiol. 277 (1999) R1690–R1696.
[45] A.R. Gosmanov, D.B. Thomason, Insulin and isoproterenol differentially regulate mitogen-activated protein kinase-dependent Na+-K+-2Cl– cotransporter activity in skeletal muscle, Diabetes 51 (2002) 615–623.
[46] T. Van Wessel, A. De Haan, W. Van der Laarse, R. Jaspers, The muscle fiber type–fiber size paradox: hypertrophy or oxidative metabolism?, Eur. J. Appl. Physiol. 110 (2010) 665–694.
[47] S. Lewis, F. Kelly, D. Goldspink, Pre-and post-natal growth and protein turnover in smooth muscle, heart and slow-and fast-twitch skeletal muscles of the rat, Biochem. J. 217 (1984) 517–526.