ORIGINAL RESEARCH

CURRENT DEVELOPMENTS IN NUTRITION

Eating Behavior and Qualitative Assessments

Time Restriction of Food Intake During the Circadian Cycle Is a Possible Regulator of Reproductive Function in Postadolescent Female Rats

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ABSTRACT

Background: We previously reported that skipping breakfast is associated with menstrual disorders of female college students during postadolescent maturation.

Objective: In this study, we investigated the effects of meal timing during circadian cycle on the ovarian function using young female rats.

Methods: Considering that rats are nocturnally active, 8-wk-old female Wistar rats were classified into 3 groups: fed during the daytime only (nonactive phase), night-time only (active phase), or control group I (without time or calorie restriction, free access to a standard caloric diet, 20.0% protein, 62.9% carbohydrate, and 7.0% fat, 3.95 kcal/g) for 4 wk. The changes in body weight and frequency of ovulation in each group were evaluated by a weight scale and a vaginal smear, respectively. At the end of the period of dietary restriction, ovaries were removed, and the numbers of growing follicles (mean diameter >250 μm) and corpora lutea (>600 μm) were examined using hematoxylin-eosin-stained tissue sections. In addition, 8-wk-old female rats were fed only during the night-time for 4 wk under a 20%-reduced food supply of the control group II (without any restriction).

Results: In the daytime-fed group, the frequency and number of ovulations were significantly decreased compared with those in the control group I ($P < 0.05$), with a reduced body weight gain concomitant with about 20% of reduction in the daily food intake. In contrast, in the night-time-fed group, even when a 20% reduction in the daily food intake was loaded, their estrus cyclicity did not change despite significant reductions in weight gain and food intake compared with control group II.

Conclusion: These findings indicate that restricting food intake to the inactive phase impairs ovarian function in postadolescent female rats, suggesting that the timing of food intake during circadian cycle is one of the crucial factors interfering with the reproductive function. *Curr Dev Nutr* 2019;3:nzy093.

Introduction

One of the most common nutritional issues among young women is insufficient energy intake and/or inappropriate food selection due to dietary limitations for cosmetic reasons and so on (1, 2). Although accumulating data indicate that adequate calorie restriction improves human health (3, 4), it is also well accepted that excess dieting can induce several menstrual disorders (5). Furthermore, because meal-skipping rates are high during young adulthood, an increase in the future risk of chronic diseases caused by these dietary behaviors has become a critical issue

Keywords: active phase, circadian rhythms, dietary restriction, ovarian function, postadolescent rat, weight gain

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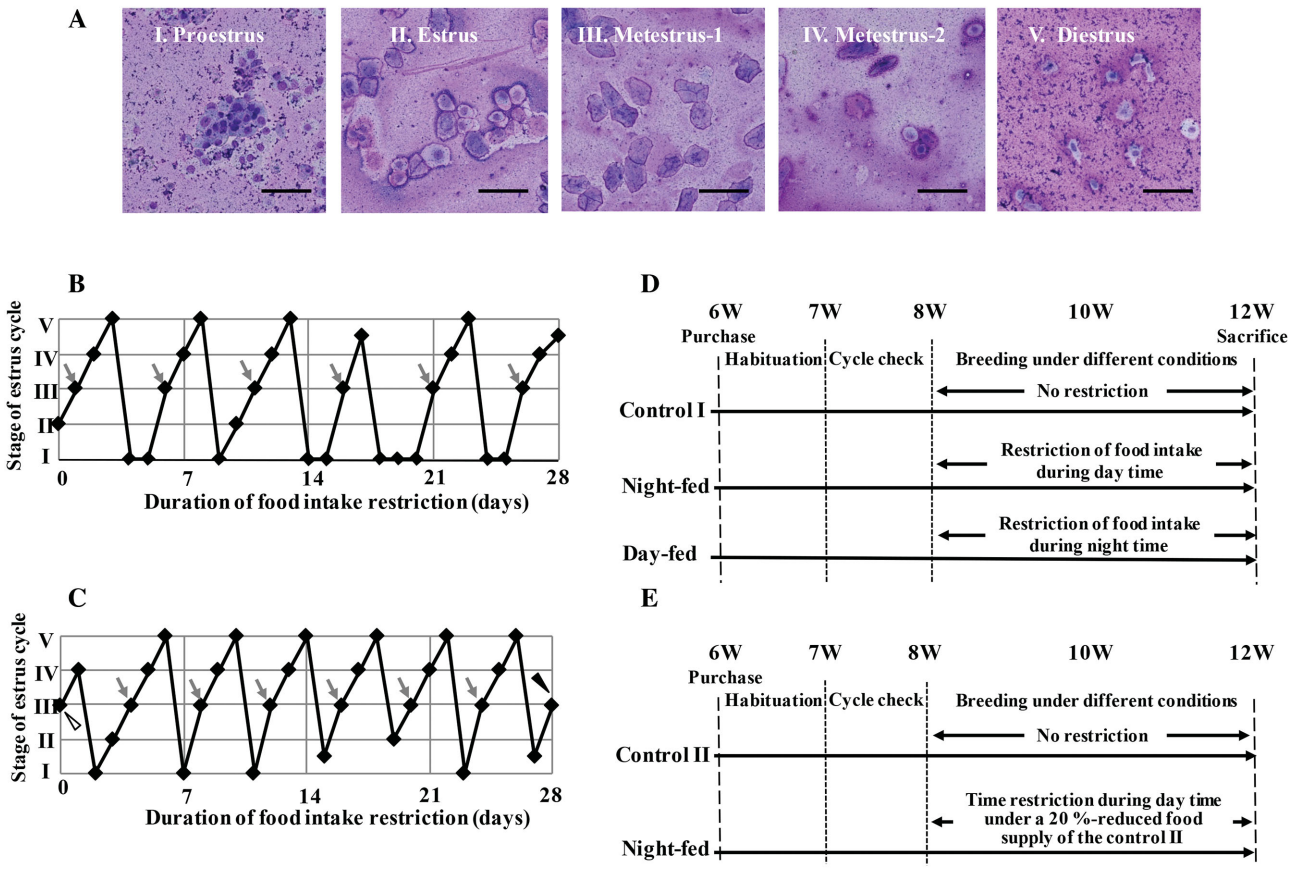

FIGURE 1 Evaluation of estrus cycle by a vaginal smear method. (A–C) Results in graphic form showing vaginal smear method and the estrus cycle. In (A), the stage of the estrus cycle was classified into 5 phases: I, proestrus; II, estrus; III, metestrus-1; IV, metestrus-2; V, diestrus using Giemsa staining. In (B) and (C), the transition from the proestrus phase (I) to estrus phase (II) or metestrus phase (III and IV) (gray arrows) was considered to be evidence of the occurrence of ovulation during the estrus cycle. In (C), the metestrus phase (III) on day 0 was not counted (white arrowhead), whereas the metestrus phase on day 28 was evaluated as evidence of ovulation (black arrowhead). Bars show 25 μm. (D) Experimental strategy for Experiment I. (E) Experimental strategy for Experiment II. Night-fed, night-time-fed group; Day-fed, daytime-fed group; W, weeks.

for young people (6). Over the last few decades, we have reported that young women who skip breakfast showed a significantly higher incidence of dysmenorrhea than those who eat breakfast (7). Similar findings were generated by a longitudinal questionnaire-based investigation, warning of the harmful effects of skipping breakfast on the reproductive function of female college students who are undergoing postadolescent maturation processes (8). Very recently, it was reported that skipping breakfast was the strongest predictor for moderate/severe dysmenorrhea among Palestinian female university students (9).

A subsequent study showed a significantly higher incidence of irregular menstruation in a group that skipped breakfast, suggesting that skipping breakfast can adversely affect the ovarian function in young women (10). However, there was no reduction in BMI, suggesting that breakfast skipping did not reduce the total supply of energy (7, 11). From these findings, we speculate that skipping breakfast interferes with the start of the active phase during circadian rhythms, and hypothesized that skipping meals at the active phase affects female reproductive functions.

In this study, to investigate the above hypothesis, we performed animal experiments using young female rats whose food intake was restricted during active and nonactive phases, and observed the effects of the timing of food intake during the circadian cycle on the reproductive function.

Methods

Animals

Six-week-old female Wistar rats ($n = 41$) were purchased from Japan SLC Ltd, and all rats were housed individually in stainless cages (W150 × L210 × H170 mm) on a normal 12-h light/dark schedule. The rats were acclimated for 1 wk, during which time they were fed a commercial laboratory diet (Certified Diet MF, Oriental Yeast Co. Ltd). During the following week, the rats were fed a standard caloric diet (AIN93-G, 20.0% protein, 62.9% carbohydrate, and 7.0% fat, 3.95 kcal/g), and the stability of their estrus cycle, which corresponds to the postadolescent stage, was confirmed as described below. Food and water were available ad libitum (12).

All experimental procedures and housing conditions were approved by Nara Women's University Animal Care Committee, and all animals

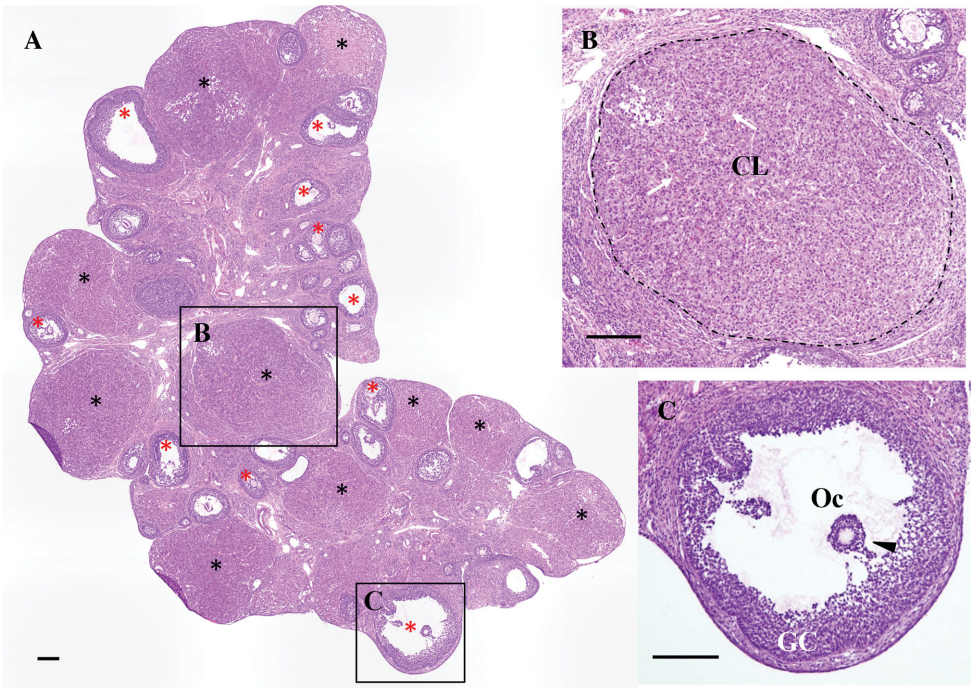

FIGURE 2 Morphological evaluation of follicles and corpora lutea of the control ovary. (A) Healthy follicles no less than 250 μm in mean diameter (red asterisks) and corpora lutea no less than 600 μm in mean diameter (black asterisks). (B) Magnified image of the corpus luteum (dotted line). Vascular network within the corpus luteum was observed (white arrows). (C) Preovulatory follicle containing an oocyte and cumulus (black arrowhead). CL, corpus luteum; GC, granulosa cells; Oc, oocyte. Bars: 200 μm.

were treated in accordance with the Institutional Guidelines for Experiments Using Animals.

Timing and calorie restriction of of food intake

Experiment I.

After the prebreeding period of 2 wk, 8-wk-old female rats were classified into 3 groups: 1) a control group that was fed without time restriction (control group I, $n = 11$, free access to a standard caloric diet), 2) a daytime-fed group that was fed only during the daytime (0800–2000, restriction of the timing of food intake during active phase to standard caloric diet, $n = 10$), and 3) a night-time-fed group that was fed only during the night-time (2000–0800, restriction of the timing of food intake during nonactive phase to standard caloric diet, $n = 10$) for 4 wk (**Figure 1**D). Throughout the experimental period, the body weight and amount of food ingested by each rat were measured daily using a scale balance (GF-6100, A&D Company, Ltd).

Experiment II.

To evaluate the possible involvement of calorie reduction in reproductive dysfunction observed in the daytime-fed group in Experiment 1, which showed approximately 20% reduction in food intake, we further loaded a 20%-reduced daily food supply on the night-time-fed group. As a control, 8-wk-old female rats ($n = 5$) were fed without time or calorie restriction for 4 wk (control group II, free access to a standard caloric diet). On the other hand, as a night-time-fed group, 8-wk-old female rats ($n = 4$) were fed only during the night-time (2000–0800) for 4 wk under a 20%-reduced food supply of the control group II (Figure 1E). The 20%-reduced feed dosage in the night-time-fed group was calculated based on the total food intake of the day before in the control group II.

Evaluation of estrus cycle

The stage of the estrus cycle was evaluated every day by a vaginal smear method (13). Using Giemsa staining, the stage was classified into 5 phases: I, proestrus; II, estrus; III, metestrus-1; IV, metestrus-2; V, diestrus (Figure 1A). The transition from the proestrus phase (I) or estrus phase (II) to metestrus phase (III and IV) (Figure 1B and C, arrows) was considered to be evidence of the occurrence of ovulation during the estrus cycle. In Experiment I, the differences in the frequency of ovulation between early (9–10-wk-old) and late (11–12-wk-old) phases were further evaluated.

Evaluation of healthy growing follicles and postovulatory corpora lutea

After the 4-wk restriction of food intake, the rats were killed under anesthesia, and the bilateral ovaries were removed and fixed by 10% formalin. Ovaries were embedded in paraffin in parallel to their long axis. Four-micrometer-thick tissue slides containing the broadest ovarian tissue section were prepared from paraffin-embedded ovary block and stained by hematoxylin-eosin staining. Images were captured using an Olympus BX50 microscope, a DP72 Olympus digital camera, and CellSens standard 1.5 software (Olympus). Initial selections of follicles (mean diameter, >250 μm) and corpora lutea (>600 μm) were performed based on their sizes using low-magnification digital photographs and the corresponding scale bars (**Figure 2**A). Next, the healthy growing follicles and corpora lutea were independently

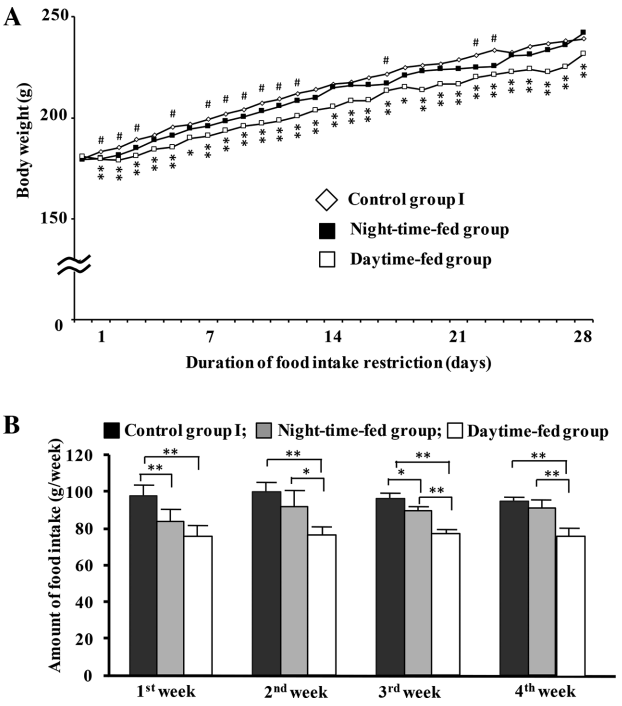

FIGURE 3 Gain in body weight and amount of food intake during dietary restriction. (A) Daily changes in body weight of the control I, night-time-fed, and daytime-fed groups during dietary restriction. The gain in body weight of the daytime-fed group was significantly reduced compared with the control I and night-time-fed groups. $^{**}P < 0.01$; $^{*}P < 0.05$ (control group I compared with daytime-fed group); $\#P < 0.05$ (control group I compared with night-time-fed group). (B) Weekly amount of food intake also decreased in the daytime-fed group. $^{**}P < 0.01$; $^{*}P < 0.05$.

evaluated under a microscope by 3 gynecologic endocrinologists (14) without any information about the origin of each slide (Figure 2B and C), and then their numbers were finally determined (Figure 2A, asterisks). If the judgment of health conditions differed, the less favorable evaluation was selected, as reported previously (15, 16).

Statistical analysis

Differences in the body weight and weight gain among the 3 groups (Experiment I) were analyzed by ANOVA, followed by a Scheffé test, and those between 2 groups (Experiment II) were evaluated by the *t*-test. The data are shown as the mean ± SD. Differences in numbers of ovulations, follicles, and corpora lutea were analyzed by the Kruskal–Wallis and Mann–Whitney test. *P* values less than 0.05 were considered to be significant. The data are shown as the median and interquartile range.

Results

Body weight gain

In Experiment I, although the body weight of the rats was gradually increased during the 4-wk period of food intake restriction in all 3 groups (**Figure 3**A), the gain of body weight in the daytime-fed group was significantly lower than in the control I and night-time-fed groups (**Table 1**). Consistent with this reduction, the weekly amount of food intake in the daytime-fed group was significantly lower than those in the control I and night-time-fed groups (Figure 3B). The mean food intake in the daytime-fed group was 78.2% of that in the control group I.

Frequency of ovulation

In Experiment I, the frequency of ovulation during time restriction of food intake was evaluated by a vaginal smear method. The frequency of ovulation in the daytime-fed group was significantly lower than those in the control I and night-time-fed groups (Table 1). When the restriction period was divided into early and late phases, the frequency of ovulation in the night-time-fed group was significantly increased in the second half of the restriction period, whereas no difference was observed in either the control group I or daytime-fed group (Table 1).

Evaluation of healthy growing follicles and postovulatory corpora lutea

In Experiment I, there were no significant differences in the numbers of healthy follicles of no less than 250 μm in diameter among the 3 groups (**Table 2**). When the cytological or layerlike morphology of granulosa cells and/or oocytes was abnormal, these follicles were omitted from the group of healthy follicles (17). In contrast, the number of corpora lutea in the daytime-fed group was significantly lower than the control I group (Table 2).

Effects of calorie restriction on frequency of ovulation in the night-time-fed rats

In Experiment II, the gain of body weight in the 20%-reduced night-time-fed group (25.6 ± 3.24 g) was significantly lower than that in the control group II (65.2 ± 5.59 g) (**Figure 4**A). In accordance with the above results, the weekly amount of food intake in the night-time-fed group was significantly lower than that in the control group II (Figure 4B). The mean final food intake in the night-time-fed group was

TABLE 1 Effects of time restriction of food intake on body weight gain and frequency of ovulation[1]

Group	Weight gain, g	Frequency of ovulation, *n*		
		Total	Early period	Late period
Control I (*n* = 11)	58.2 ± 9.8**	6 (6–7)*	3 (3–3)	3 (3–4)
Night-time-fed (*n* = 10)	56.6 ± 11.6*,**	6 (6–6)*,**	3 (3–3)*	3 (3–4)
Daytime-fed (*n* = 10)	44.6 ± 10.0*,**	5 (5–6)*,**	3 (2–3)	3 (2–3)

[1]The restriction period was divided into early (9–10-wk-old) and late phases (11–12-wk-old). Weight gain and frequency of ovulation are expressed as mean ± SD and the median and interquartile range, respectively. $^{**}P < 0.01$; $^{*}P < 0.05$.

72.4% of that in the control group II. Despite marked reductions in the calorie intake and subsequent body weight gain, there was no difference in estrus cyclicity between the 2 groups (Figure 4C, shown as the median and interquartile range).

Discussion

In this study, we examined the relation between the timing of food intake during the circadian cycle and reproductive function during the estrus cycle by animal experiments. There were no differences in the frequency of ovulation between the control I and night-time-fed groups (Table 1), indicating that restriction of the timing of food intake in the nonactive phase did not affect the estrus cycle. However, when we limited the timing of food intake to the daytime (restricted food intake during nonactive phase), the frequency of ovulation in the daytime-fed group was significantly reduced compared with those in the control I and night-time-fed groups (Table 1). This study also demonstrated that the number of corpora lutea, the size of which was over 600 μm, was significantly decreased in the daytime-fed group among the 3 groups (Table 2). Because these mature healthy corpora lutea are considered to be derived from the follicles that were freshly ovulated during the near estrus cycles, we deduced that the number of ovulating follicles per cycle had declined in the daytime-fed group. From these findings, we conclude that the difference in timing of food intake during the active or nonactive phase is a crucial factor that influences the female reproductive function.

In Experiment I, the night-time-fed group showed compensation for the reduction in food intake and thereby normalized the gain in body weight. Because the amount of food intake in the night-time-fed group gradually increased during the restricted time (Figure 3B), the increase in food intake may be one of the main factors that improved body weight gain. In contrast, there was a significant reduction in the gain in body weight and amount of food intake in the daytime-fed group (Figure 3). Therefore, it is possible that a reduction in calorie intake induces reproductive dysfunction in the daytime-fed group. The mean total reduction in food intake in the daytime-fed group was 21.8% compared with that of the control group I (Figure 3). Accordingly, to evaluate the possible involvement of caloric limitation in the reproductive dysfunction observed in our animal models, we further observed the effects of equivalent caloric restriction on the frequency of ovulation using night-time-fed rats under more than 25% caloric reduction. Notably, no significant change in estrus cyclicity was observed despite the reduction in the amount of food intake and gain in body weight. These findings indicate that reproductive dysfunction was mainly induced not by an insufficient calorie intake, but by the differences in the timing of food intake during the daytime or night-time.

TABLE 2 Effects of time restriction of food intake on numbers of follicles and corpora lutea[1]

Group	Follicles, *n*	Corpora lutea, *n*
Control I ($n = 11$)	11 (9–13)	11 (9–12)*
Night-time-fed ($n = 10$)	11 (10–14)	9.5 (8.5–11.5)*
Daytime-fed ($n = 10$)	10 (8–12)	8.5 (7–9.5)*

[1]Numbers of follicles and corpora lutea were expressed as the median and interquartile range. *$P < 0.05$.

In general, either the reduction in numbers of ovulated follicles or a decreased frequency of ovulation represents a disorder of the hypothalamic–pituitary–ovarian axis (18, 19). Recently, attention has focused on the relation between the circadian rhythm and reproductive function (20). Circadian rhythms are created by a synchronized transcriptional oscillators or molecular clocks that are encoded by clock genes such as brain and muscle ARNT-like 1 (*Bmal1*), *Clock*, *Period*, and *Cryptochrome* (21). The hypothalamic suprachiasmatic nucleus, which is mainly entrained by light/dark cycles, acts as a master pacemaker for circadian behavioral rhythms in mammals (22), whereas peripheral oscillators, which can be affected by daily feeding cycles, are present in most body cells (23). The deficiency of clock genes in mice was reported to attenuate reproductive functions such as ovarian steroidogenesis, estrous cyclicity, and the maintenance of pregnancy (24, 25). Deletion of the *Bmal1* gene showed a reduction in progesterone production, resulting in complete implantation failure in female mice (26, 27). This gene was also reported to regulate the timing of ovulation by controlling the phasic sensitivity of follicles to gonadotropins (28). On the other hand, a recent study showed that feeding at an unusual time of day (inactive phase) desynchronizes peripheral clocks, causing obesity and metabolic disorders in adult mice (29). Accordingly, we should consider the possibility that the differences between daytime-fed and night-time-fed groups are partially derived from disturbance of the clock gene system.

To support the above speculation, shift-workers were reported to be at risk of reproductive disorders such as irregular menses, endometriosis, infertility, miscarriage, low birth weight or preterm delivery, and reduced incidence of breastfeeding (30, 31). It should be noted that food intake is another important stimulator that can reset the central circadian rhythm in the brain and peripheral clocks in the digestive organs (23, 32). Actually, shift work is associated with increased risks of obesity, diabetes, and cardiovascular diseases as a result of unusual eating time and disruption of the circadian rhythm (33). Although the day and night are reversed in shift-workers, the timing of food intake is synchronous with their active behaviors. In contrast, the phase of food intake dose not coincide with active behaviors in skipping breakfast and our animal experiments. Consequently, the constant asynchrony between light stimulation and food intake during active behaviors may chronically affect the central and/or peripheral clock systems. In this study, the reduction in ovulatory frequency was continuously manifested even in the second half of the dietary restriction period in the daytime-fed group (Table 1), suggesting that daytime-feeding is a constant stress on the hypothalamic–pituitary–ovarian axis. On the other hand, although there was no difference in the total frequency of ovulation between the control I and night-time-fed groups, ovulation increased from early to late period in the night-time-fed group (Table 1), suggesting the recovery from the initial stress of dietary restriction in the night-time-fed group. Furthermore, this group showed no change in estrus cyclicity despite a considerable reduction in calorie intake (Figure 4C), demonstrating a marked difference between the daytime-fed and night-time-fed groups. It may be because food intake during the night-time only is compatible with the normal behavior of rats, which are active at night in the natural world.

Importantly, this study also demonstrates apparent differences in the amount of food intake between the daytime- and night-time-fed

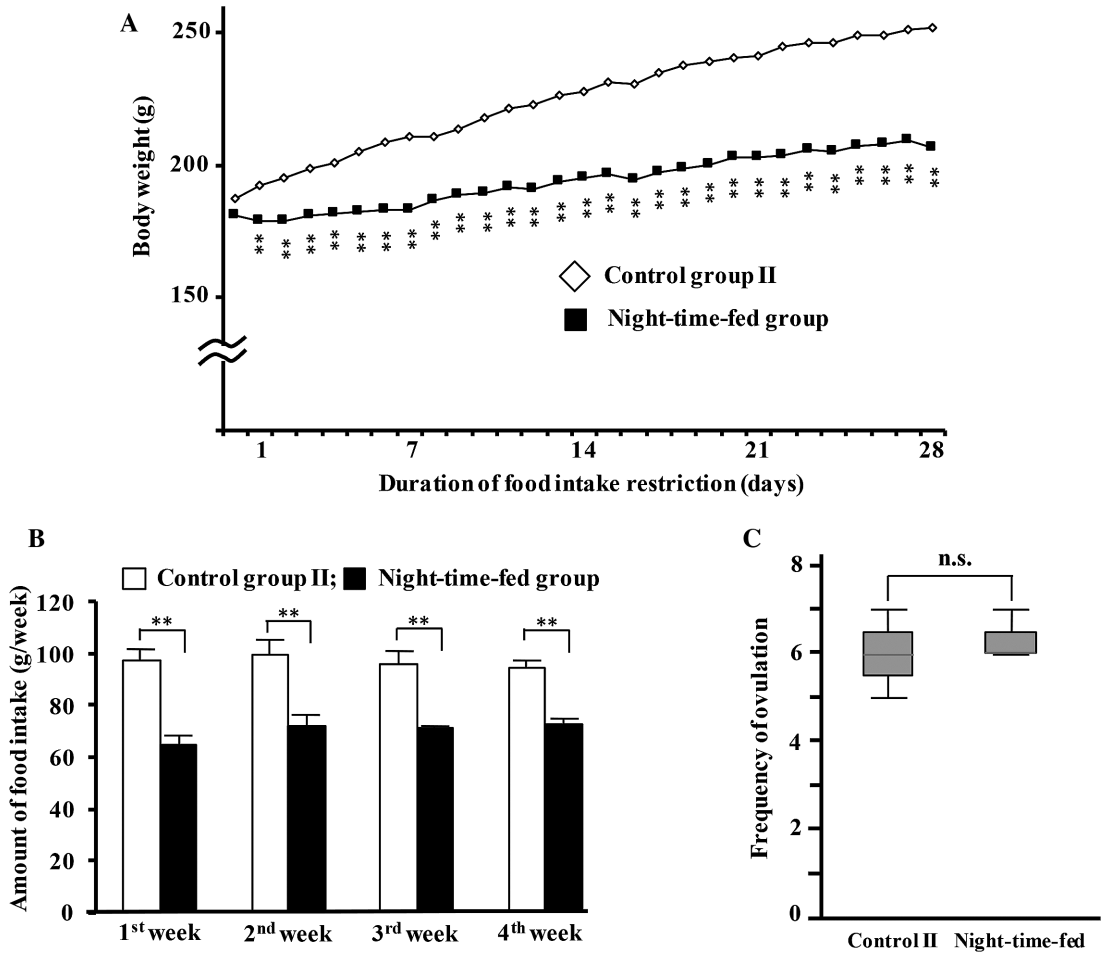

FIGURE 4 Effects of calorie restriction in the night-time-fed rats. To evaluate the possible involvement of calorie restriction in reproductive dysfunction, a 20% reduction in daily food supply was loaded on the night-time-fed group. (A) Growing curve of body weight. Gain in body weight of the 20%-reduced night-time-fed group was significantly lower than that in the control group II. (B) Amount of food intake. In accordance with A, weekly amount of food intake in the night-time-fed group was significantly lower than that in the control group II. The mean final food intake in the night-time-fed group was 72.4% of that in the control group II. (C) Ovulation numbers shown as the median and interquartile range in the 2 groups. Despite marked reductions in calorie intake and body weight gain, there was no difference in estrus cyclicity between the 2 groups. $^{**}P < 0.01$; $^{*}P < 0.05$; n.s.: not significant.

groups, with a >20% reduction in food intake in the daytime-fed group as compared with the control group I. This reduction was considered to interfere with physiological growth during the postadolescent stage and resulted in a significant reduction in body weight gain. Because appetite loss during adolescent and postadolescent phases is physiopathologically important in young women (34, 35), the precise relations among appetite loss, reproductive dysfunction, and clock gene systems should be clarified from a comprehensive perspective in the future.

Conclusions

This study demonstrated that the frequency of ovulation and number of ovulating follicles declined in the daytime-fed young female rats, indicating that the difference in timing of food intake during the active or nonactive phase is a crucial factor that influences the female reproductive function during the postadolescent stage in rats. To our knowledge, this is the first study to experimentally confirm the adverse effect of feeding at an unusual time during the circadian cycle on the female reproductive function during the estrus cycle. Although we should not apply these findings directly to humans, this model can provide valuable information to clarify the mechanisms explaining why female young students who skip breakfast show reproductive dysfunction. Because the constant conflict of light stimulation and food intake during the active phase may chronically affect circadian rhythms, the differences between daytime- and night-time-fed groups should be analyzed from the perspective of clock gene systems using conditional gene-deleted mice (36, 37). This study also suggests that feeding at an unusual time induces appetite loss in postadolescent female rats. Recently, factors inducing chronic environmental circadian disruption have become social targets to prevent adverse health outcomes (20, 38). In this regard, the adverse influence of dietary habits during the postadolescent phase on the future fertility and appetite-related adult diseases is also a critical issue that should be elucidated.

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References

1. Das JK, Salam RA, Thornburg KL, Prentice AM, Campisi S, Lassi ZS, Koletzko B, Bhutta ZA. Nutrition in adolescents: Physiology, metabolism, and nutritional needs. Ann NY Acad Sci 2017;1393:21–33.
2. Fujiwara T. Diet during adolescence is a trigger for subsequent development of dysmenorrhea in young women. Int J Food Sci Nutr 2007;58:437–44.
3. Wärnberg J, Nova E, Romeo J, Moreno LA, Sjöström M, Marcos A. Lifestyle-related determinants of inflammation in adolescence. Br J Nutr 2007;98(Suppl 1):S116–120.
4. Most J, Tosti V, Redman LM, Fontana L. Calorie restriction in humans: An update. Ageing Res Rev 2017;39:36–45.
5. Nazni P. Association of western diet and lifestyle with decreased fertility. Indian J Med Res 2014;140(Suppl):S78–81.
6. Pendergast FJ, Livingstone KM, Worsley A, McNaughton SA. Correlates of meal skipping in young adults: A systematic review. Int J Behav Nutr Phys Act 2016;13:125.
7. Fujiwara T. Skipping breakfast is associated with dysmenorrhea in young women in Japan. Int J Food Sci Nutr 2003;54:505–9.
8. Fujiwara T, Nakata R. Skipping breakfast is associated with reproductive dysfunction in post-adolescent female college students. Appetite 2010;55:714–7.
9. Abu Helwa HA, Mitaeb AA, Al-Hamshri S, Sweileh WM. Prevalence of dysmenorrhea and predictors of its pain intensity among Palestinian female university students. BMC Women's Health 2018;18:18.
10. Fujiwara T, Sato N, Awaji H, Sakamoto H, Nakata R. Skipping breakfast adversely affects menstrual disorders in young college students. Int J Food Sci Nutr 2009;60(Suppl 6):23–31.
11. Okada C, Tabuchi T, Iso H. Association between skipping breakfast in parents and children and childhood overweight/obesity among children: A nationwide 10.5-year prospective study in Japan. Int J Obes (Lond) 2018;42(10):1724–32.
12. Yagisawa M, Okawa N, Shigematsu N, Nakata R. Effects of intravenous betaine on methionine-loading-induced plasma homocysteine elevation in rats. J Nutr Biochem 2004;15:666–71.
13. Cora MC, Kooistra L, Travlos G. Vaginal cytology of the laboratory rat and mouse: Review and criteria for the staging of the estrous cycle using stained vaginal smears. Toxicol Pathol 2015;43:776–93.
14. Hirshfield AN. Compensatory ovarian hypertrophy in the long-term hemicastrate rat: Size distribution of growing and atretic follicles. Biol Reprod 1983;28:271–8.
15. Fujiwara H, Ueda M, Hattori N, Mori T, Maeda M. A differentiation antigen of human large luteal cells in corpora lutea of the menstrual cycle and early pregnancy. Biol Reprod 1996;54:1173–83.
16. Iizuka T, Wakae K, Nakamura M, Kitamura K, Ono M, Fujiwara H, Muramatsu M. APOBEC3G is increasingly expressed on the human uterine cervical intraepithelial neoplasia along with disease progression. Am J Reprod Immunol 2017;78:e12703.
17. Fujiwara H, Ueda M, Fukuoka M, Yasuda K, Imai K, Takakura K, Kanzaki H, Suginami H, Mori T, Maeda M. A new monoclonal antibody (POG-1) detects a differentiation antigen of porcine granulosa and thecal cells and indicates heterogeneity of thecal-stromal cells. Endocrinology 1994;134:1132–8.
18. Baerwald AR, Adams GP, Pierson RA. Ovarian antral folliculogenesis during the human menstrual cycle: A review. Hum Reprod Update 2012;18:73–91.
19. Assadullah, Ieda N, Kawai N, Ishii H, Ihara K, Inoue N, Uenoyama Y, Tsukamura H. Co-expression of the calcitonin receptor gene in the hypothalamic kisspeptin neurons in female rats. Reprod Med Biol 2018;17:164–72.
20. Sen A, Sellix MT. The circadian timing system and environmental circadian disruption: From follicles to fertility. Endocrinology 2016;157:3366–73.
21. Mohawk JA, Green CB, Takahashi JS. Central and peripheral circadian clocks in mammals. Annu Rev Neurosci 2012;35:445–62.
22. Mieda M, Ono D, Hasegawa E, Okamoto H, Honma K, Honma S, Sakurai T. Cellular clocks in AVP neurons of the SCN are critical for interneuronal coupling regulating circadian behavior rhythm. Neuron 2015;85: 1103–16.
23. Mendoza J. Circadian clocks: Setting time by food. J Neuroendocrinol 2007;19:127–37.
24. Nakao N, Yasuo S, Nishimura A, Yamamura T, Watanabe T, Anraku T, Okano T, Fukada Y, Sharp PJ, Ebihara S, et al. Circadian clock gene regulation of steroidogenic acute regulatory protein gene expression in preovulatory ovarian follicles. Endocrinology 2007;148:3031–8.
25. Miller BH, Olson SL, Turek FW, Levine JE, Horton TH, Takahashi JS. Circadian clock mutation disrupts estrous cyclicity and maintenance of pregnancy. Curr Biol 2004;14:1367–73.
26. Ratajczak CK, Boehle KL, Muglia LJ. Impaired steroidogenesis and implantation failure in Bmal1-/- mice. Endocrinology 2009;150:1879–85.
27. Liu Y, Johnson BP, Shen AL, Wallisser JA, Krentz KJ, Moran SM, Sullivan R, Glover E, Parlow AF, Drinkwater NR, et al. Loss of BMAL1 in ovarian steroidogenic cells results in implantation failure in female mice. Proc Natl Acad Sci USA 2014;111:14295–300.
28. Mereness AL, Murphy ZC, Forrestel AC, Butler S, Ko C, Richards JS, Sellix MT. Conditional deletion of Bmal1 in ovarian theca cells disrupts ovulation in female mice. Endocrinology 2016;157:913–27.
29. Yasumoto Y, Hashimoto C, Nakao R, Yamazaki H, Hiroyama H, Nemoto T, Yamamoto S, Sakurai M, Oike H, Wada N, et al. Short-term feeding at the wrong time is sufficient to desynchronize peripheral clocks and induce obesity with hyperphagia, physical inactivity and metabolic disorders in mice. Metabolism 2016;65:714–27.
30. Labyak S, Lava S, Turek F, Zee P. Effects of shiftwork on sleep and menstrual function in nurses. Health Care Women Int 2002;23: 703–14.
31. Gamble KL, Resuehr D, Johnson CH. Shift work and circadian dysregulation of reproduction. Front Endocrinol (Lausanne) 2013; 4:92.
32. Ando H, Ushijima K, Shimba S, Fujimura A. Daily fasting blood glucose rhythm in male mice: A role of the circadian clock in the liver. Endocrinology 2016;157:463–9.
33. Engin A. Circadian rhythms in diet-induced obesity. Adv Exp Med Biol 2017;960:19–52.
34. Clarke TK, Weiss AR, Berrettini WH. The genetics of anorexia nervosa. Clin Pharmacol Ther 2012;91:181–8.
35. Misra M, Klibanski A. Endocrine consequences of anorexia nervosa. Lancet Diabetes Endocrinol 2014;2:581–92.
36. Daikoku T, Dey SK. Two faces of PTEN. Nat Med 2008;14:1192–3.
37. Daikoku T, Cha J, Sun X, Tranguch S, Xie H, Fujita T, Hirota Y, Lydon J, DeMayo F, Maxson R, et al. Conditional deletion of Msx homeobox genes in the uterus inhibits blastocyst implantation by altering uterine receptivity. Dev Cell 2011;21:1014–25.
38. Lunn RM, Blask DE, Coogan AN, Figueiro MG, Gorman MR, Hall JE, Hansen J, Nelson RJ, Panda S, Smolensky MH, et al. Health consequences of electric lighting practices in the modern world: A report on the National Toxicology Program's workshop on shift work at night, artificial light at night, and circadian disruption. Sci Total Environ 2017;31:1073–84.