Short and long photoperiods differentially exacerbate corticosterone-induced physical and psychological symptoms in mice

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ABSTRACT

Circadian disruption affects the pathogenesis and development of various diseases. Depression is one of the most common diseases that relate to circadian rhythm. In this study, we analyzed the effects of daily light/dark (LD) conditions on depression and other symptoms, and also analyzed the mixed effects of LD conditions and corticosterone treatment. Male adult C57BL/6 mice were treated with corticosterone in a normal LD cycle of 12 hours light and 12 hours dark (LD12 : 12), short day conditions of 6 hours light and 18 hours dark (LD6 : 18), or long day conditions of 21 hours light and 3 hours dark (LD21 : 3). The activity rhythms of mice in aberrant LD conditions were entrained within 2 weeks. After 6 weeks of exposure, several behavioral tests were conducted. Corticosterone induced body weight gain and depression-like symptoms. The short or long LD conditions had little effect on vehicle-treated mice behavior. However, the aberrant LD conditions exacerbated the corticosterone-induced symptoms. Mice treated with corticosterone in LD6 : 18 showed exacerbated depression-like symptoms in a novelty suppressed feeding test. On the other hand, LD21 : 3 did not show any effects on mood, but enhanced corticosterone-induced body weight gain. These results indicated that aberrant LD conditions could act as an exacerbating factor for corticosterone-induced symptoms, and that short and long photoperiods induce different psychological and physiological changes. This corticosterone + aberrant LD model could be a useful animal model for investigating the effect of LD conditions on depression, obesity, and other symptoms in stressful circumstances.

Biological rhythm governs almost all mammalian organs. Impairment of the rhythms causes dysfunction in various organs, sometimes leading to diseases such as insomnia, cancer, diabetes, and affective mood disorders (18, 26). Genetic disruption of the circadian clock system induces various disease-like symptoms in laboratory rodents. *Clock* mutant mice develop obesity and metabolic syndrome (30). Knockdown of *Clock* in the ventral tegmental area induces bipolar disorder-like symptoms (22). Circa-

dian disruption should be considered an important risk factor for various diseases.

Circadian rhythm is controlled not only by clock genes but also by environmental factors such as the light/dark (LD) cycle, feeding, and social activities (18, 26). Light is the most influential environmental factor in the phases of circadian rhythms. The abnormal manipulation of the daily LD conditions disrupts the circadian system and sometimes causes diseases. Previous studies indicated that chronic exposure to aberrant LD conditions such as constant light, constant dark, and repeated phase shifts induces physical and/or psychological impairment in genetically intact rats and mice (7, 17, 21, 28, 29).

Depression is one of the most common diseases that relate to circadian rhythm. Seasonal affective

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disorder (SAD) is a type of depression characterized by depression and other symptoms during a specific season, usually winter (24). Length of lighting period in a day might contribute to the pathogenesis of SAD. Various animal models for the analysis of SAD have been developed by modifying daily LD conditions. Previous studies revealed that a chronic short photoperiod induces depression-like symptoms in some rodents (32). Several studies suggested that diurnal rodents such as sand rat and grass rat were more sensitive to the photoperiod than nocturnal rodents, and were advantageous as SAD models (2, 10, 11). On the other hand, melatonin-deficient laboratory mice such as C57BL/6 were thought to be inappropriate for a model of SAD (32). Recently, however, Otsuka *et al.* showed that C57BL/6 mice in a short photoperiod showed depression-like symptoms (23). They discussed that the melatonin-independent pathway might play an important role in inducing SAD in C57BL/6 mice.

Long and short photoperiods should have some impacts on mood, but there are conflicting reports about the effect of aberrant photoperiods. Although many studies showed that a short photoperiod induced depression-like symptoms, some studies showed inconsistent results. Flaisher-Grinberg *et al.* reported that C57BL/6 and CD-1 mice did not show clear depression- and anxiety-like behavior under a long or short photoperiod (11). Dulcis *et al.* reported that a long photoperiod induced depression-like symptoms and a short photoperiod showed an antidepressant effect in C57BL/6 mice (9). The effect of an aberrant photoperiod may vary depending on species, strains, and experimental conditions.

In this study, we investigated the effects of short and long photoperiods on mood and other symptoms in mice. We also analyzed the mixed effect of aberrant photoperiods and corticosterone treatment on mice behavior. Corticosterone is a stress hormone, and chronic corticosterone treatment induces depressive symptoms in mice (8, 16, 27). This treatment has been widely used to develop an animal model of depression. Since people are usually exposed to various risk factors in real life, the analysis of the mixed effect of LD alteration and other risk factors should be important. We maintained male adult C57BL/6 mice in a short or long photoperiod and treated them with corticosterone for 6 weeks. We then conducted several behavioral tests to detect depression and other symptoms in mice. The exacerbating effects of the aberrant photoperiod on corticosterone-induced physical and psychological symptoms were analyzed.

MATERIALS AND METHODS

Animals. Male adult C57BL/6NCrSlc mice (20–25 g) were obtained from Japan SLC (Shizuoka, Japan) and maintained in an air-conditioned room at 24 ± 2°C with a 12 h/12 h light/dark cycle (lights on at 7 : 00 a.m.), except for mice that were exposed to other experimental LD conditions as described below. All mice had free access to food and water. Animal maintenance and treatments were in accordance with the general recommendations of animal protection legislation in Japan. All procedures were approved by the Institutional Animal Care and Use Committee of Josai International University.

Chemicals. Corticosterone and other chemicals were obtained from Wako Pure Chemical Industries (Osaka, Japan).

Treatment. After an acclimation period of at least 1 week, mice were treated with corticosterone or vehicle under the experimental LD conditions. Corticosterone was administered according to a previous report (8). Mice were exposed to corticosterone (35 μg/mL in 0.45% β-cyclodextrin) or vehicle in the drinking water during the experiment period. Mice were maintained in normal LD conditions (12 hours light and 12 hours dark, LD12 : 12), short day conditions (6 hours light and 18 hours dark, LD6 : 18), or long day conditions (21 hours light and 3 hours dark, LD21 : 3).

The experimental schedules and groups are shown in Fig. 1. The mice were divided into four groups: control, CORT (corticosterone), LDx (aberrant LD conditions), and CORT+LDx. The control and LDx groups were treated with vehicle, while the CORT and CORT+LDx groups were treated with corticosterone. The control and CORT groups were maintained in LD12 : 12, while the LDx and CORT+LDx groups were maintained in LD6 : 18 (experiment 1) or LD21 : 3 (experiment 2). After 6 weeks of exposure, behavioral tests were carried out. An open field test, LD box test, tail suspension test, and novelty suppressed feeding test were carried out in this order on the 7th week. All behavioral tests were conducted during the early light period (8 : 00 am to 11 : 00 am).

Activity rhythm in home cage. Mice were individually housed in their home cages, and were continuously monitored with infrared sensors (Supermex; Muromachi Kikai, Tokyo, Japan). The locomotor activity of each mouse was observed in a 1 min bin
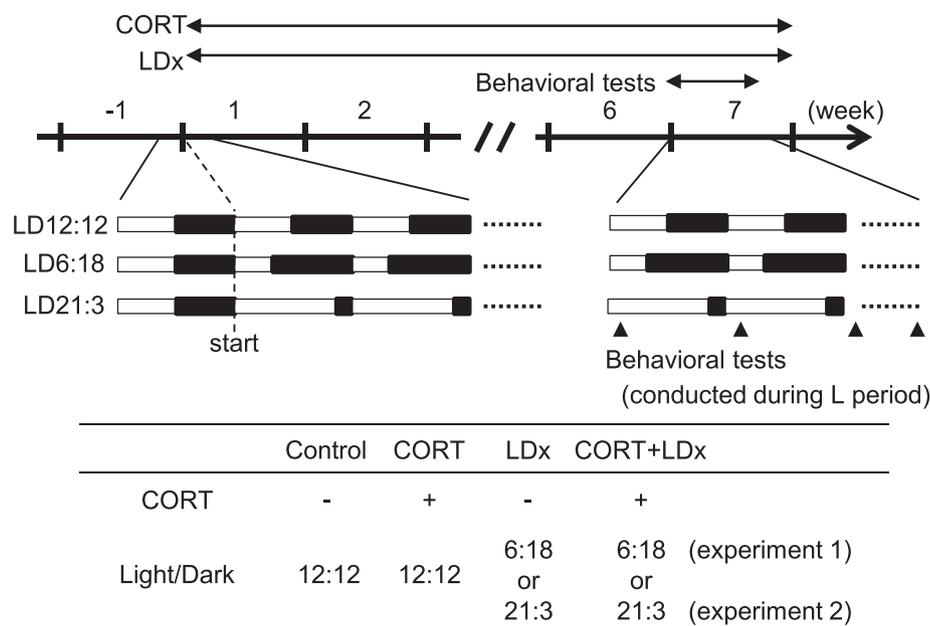
Fig. 1 Experimental schedule and groups. Mice were treated with corticosterone or vehicle under respective LD conditions. Arrows at the top represent the periods of corticosterone treatment (CORT), aberrant photoperiod (LDx), and behavioral tests. Black and white bars represent light and dark periods in the day, respectively. Experimental conditions in each group are shown in the table at the bottom.

	Control	CORT	LDx	CORT+LDx
CORT	-	+	-	+
Light/Dark	12:12	12:12	6:18 or 21:3	6:18 (experiment 1) or 21:3 (experiment 2)

using CompACT AMS software (Muromachi Kikai).

Open field test. The test was conducted in a darkened room. The apparatus consisted of an opaque plastic field (80 cm diameter and 30 cm height), the bottom of which was divided into 19 areas, with a light (60 W) at 50 cm above the bottom. A mouse was placed at the edge of the field, and its locomotor activity was observed for 3 min. The number of divided areas in which the mouse traversed was counted as an ambulation score, and the total duration that the mouse was in the center area of the field was scored as an index of anxiety.

Light/dark box test. The test was conducted in a darkened room. The apparatus consisted of a rectangular plastic chamber (40 × 20 × 20 cm) separated by a partition with a small opening. One side had a clear roof (light side) and the other had a fully opaque roof and side walls (dark side). The light side was illuminated with a 60 W light. A mouse was placed in the dark side, and the number of times it entered the light side, as well as the total duration of its presence in that side, were recorded for 5 min. These scores were evaluated as indices of anxiety, with lower scores indicating greater anxiety.

Tail suspension test. Mice were hung individually on a bar using a paper adhesive tape at 35 cm above a table. The adhesive tape was placed 2–3 cm from the tip of the tail. Each mouse was suspended for 6 min, and the duration of immobility was measured by a trained observer. Immobility was defined as an absence of body movement during the session and was evaluated as an index of depression, with longer immobility indicating depression.

Novelty suppressed feeding test. Mice were starved for 24 h before the test. The test field consisted of a plastic box (40 × 20 × 20 cm), the floor of which was covered with approximately 2 cm bedding. A pellet of mouse food was placed on a white paper platform (90 mm diameter) in the center of the field. The test room was darkened and the test field was illuminated with a 60 W light at 50 cm above the bottom. A mouse was placed in a corner of the field, and the latency to eat the pellet was measured by a trained observer. Eating was defined as the mouse sitting on its haunches and biting the pellet while holding the pellet in its forepaws. If the mouse did not eat the pellet for 10 min, latency was scored 10 min. Increased latency was evaluated as an index of depression.

Statistical analysis. Data are expressed as means ± SEM. The main effect of corticosterone treatment

(A) LD12:12

12:12
12:12
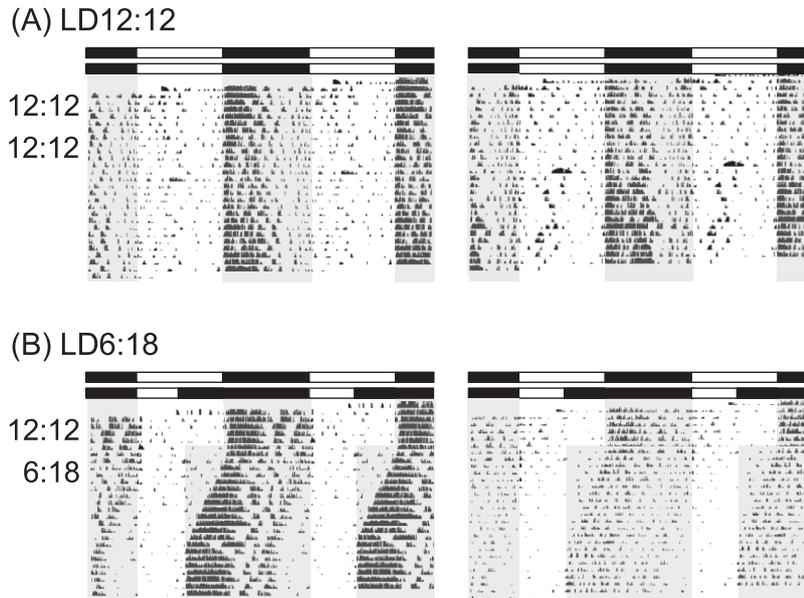
(B) LD6:18

12:12
6:18

Fig. 2 Activity rhythm of mice in the short photoperiod. Representative double-plotted actograms of mice in LD12 : 12 and LD6 : 18 are shown. The mice were maintained in the normal photoperiod (LD12 : 12) for 5 days, and then in the normal (A) or short (LD6 : 18, B) photoperiod. Black columns on the row represent an activity count in a 1-min bin. Each row represents a 2-day period of activity, and the graph overall represents activity during a total of 4 weeks. Horizontal white and black bars at the top represent light and dark periods, respectively, and shaded gray areas in the actogram represent dark periods.

and LD conditions singly, as well as the interaction effect of these factors together, were analyzed with two-way ANOVA (Figs. 3, 5). The differences between the group were analyzed with Tukey's test (Figs. 3, 5). The significance level was set at $P < 0.05$.

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, EZR is a modified version of the R commander that is designed to add statistical functions frequently used in biostatistics (19).

RESULTS

Experiment 1: Effects of corticosterone and short photoperiod on mouse behavior
Fig. 2 shows the effect of the short photoperiod on activity rhythms. The mice in LD6 : 18 showed advancement of the activity phase for approximately 2 weeks, and then showed stable 24-h rhythms entrained to the new LD conditions.

Mice were treated with corticosterone and/or a short photoperiod (LD6 : 18) for 6 weeks, and were analyzed with behavioral tests in the 7th week. The

results of the behavioral tests are shown in Fig. 3. The interaction effect of corticosterone and aberrant LD was detected in the tail suspension test (F = 4.590, $P = 0.038$). The main effects of corticosterone treatment were detected in body weight (F = 82.605, $P < 0.001$) and latency in the novelty suppressed feeding test (F = 29.136, $P < 0.001$). The main effects of aberrant LD were detected in ambulation in the open field test (F = 6.555, $P = 0.014$), time in center in the open field test (F = 4.606, $P = 0.037$), and latency in the novelty suppressed feeding test (F = 4.207, $P = 0.046$). Tukey's test detected statistically significant differences between groups in body weight (control vs CORT, $P < 0.001$; control vs CORT+LDx; $P < 0.001$; CORT vs LDx, $P < 0.001$; LDx vs CORT+LDx, $P < 0.001$), ambulation in the open field test (CORT vs CORT+LDx, $P = 0.017$), and latency in the novelty suppressed feeding test (control vs CORT+LDx, $P < 0.001$; CORT vs CORT+LDx, $P = 0.038$; LDx vs CORT+LDx, $P < 0.001$). Corticosterone induced body weight gain (Fig. 3A) and depression-like behavior in the novelty suppressed feeding test (Fig. 3E); whereas, the short photoperiod had no effect on body weight, but induced some changes in the open field test and the novelty suppressed feeding test (Fig. 3B, E).

Although two-way ANOVA detected the signifi-
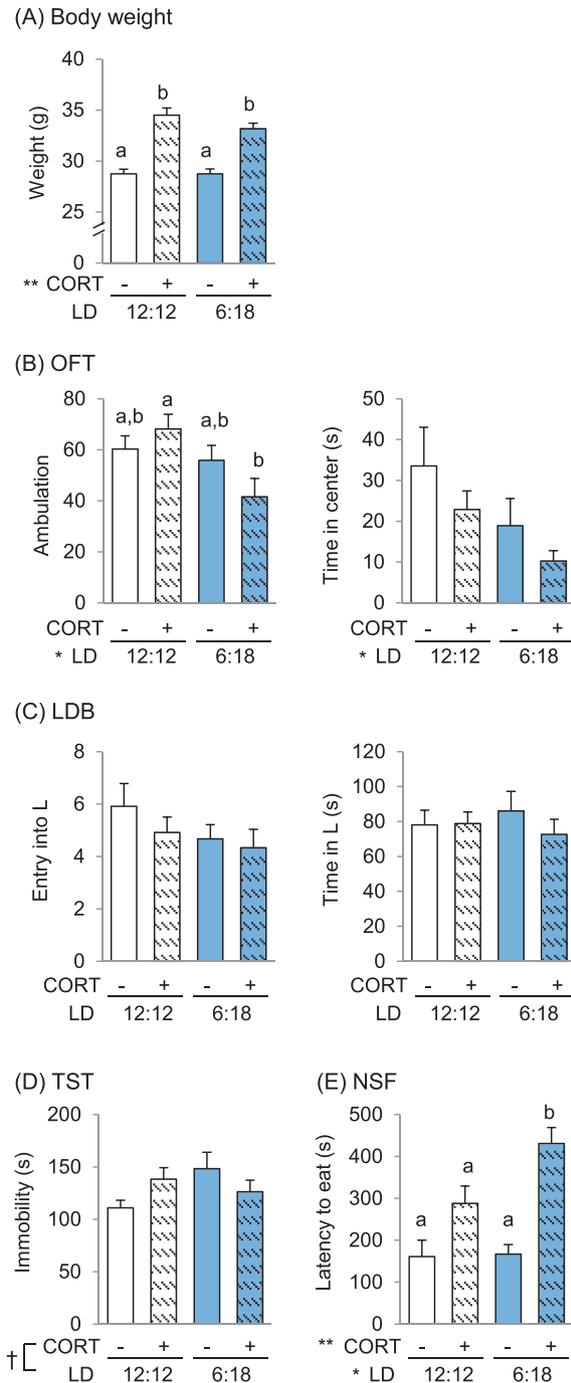
Fig. 3 Effects of corticosterone and a short photoperiod on body weight and behavior in mice. Mice were chronically treated with corticosterone or vehicle in the normal (LD12 : 12) or short (LD6 : 18) photoperiod. On the 7th week, their body weight (A) and behaviors in the open field test (OFT; B), LD box test (LDB; C), tail suspension test (TST; D), and novelty suppressed feeding test (NSF; E) were analyzed. Values are presented as means ± SEM (*n* = 12). *$P < 0.05$, **$P < 0.01$ in the main effect, †$P < 0.05$ in the interaction effect of corticosterone and aberrant LD conditions by two-way ANOVA. The different letters (a, b, c) indicate a significant difference ($P < 0.05$) by Tukey's test.

cant main effect of the short photoperiod and no interaction effect, the difference against control was larger in CORT+LD6 : 18 than LD6 : 18 in the open field test and novelty suppressed feeding test. The short photoperiod seems to have enhanced the effect of corticosterone in these tests. In particular, latency to eat in the novelty suppressed feeding test showed an almost significant interaction between corticosterone and aberrant LD conditions (F = 3.589, $P = 0.065$ by two-way ANOVA). In the absence of corticosterone, LD12 : 12 and LD6 : 18 showed almost the same scores in the novelty suppressed feeding test, suggesting that the short photoperiod alone had little effect on depression. Corticosterone increased latency in the normal LD conditions (LD12 : 12), and further increased it in the short photoperiod (LD6 : 18). These results suggest that the short photoperiod alone could not induce depression, but could reinforce the effect of corticosterone on depression.

Experiment 2: Effects of corticosterone and long photoperiod on mouse behavior
Fig. 4 shows the effect of the long photoperiod on activity rhythms. The activity rhythms of mice in LD21 : 3 seemed disordered after the change to LD21 : 3. However, the rhythms were entrained to the new LD cycle within 2 weeks, and the 24-h rhythm was maintained thereafter.

Mice were treated with corticosterone and/or a long photoperiod (LD21 : 3) for 6 weeks, and were analyzed with behavioral tests in the 7th week. The results of those tests are shown in Fig. 5. No interaction effect of corticosterone and aberrant LD was detected. The main effects of corticosterone treatment were detected in body weight (F = 21.919, $P < 0.001$), ambulation in the open field test (F = 6.288, $P = 0.017$), entry into L (light box) in the LD box test (F = 5.386, $P = 0.026$), time in L in the LD box test (F = 4.295, $P = 0.046$), and latency in the novelty suppressed feeding test (F = 6.544, $P = 0.015$). The main effect of aberrant LD conditions was detected in body weight (F = 9.713, $P = 0.004$). Tukey's test detected statistically significant differences between groups in body weight (control vs CORT, $P = 0.047$; control vs CORT+LDx; $P < 0.001$; CORT vs CORT+LDx, $P = 0.010$; LDx vs CORT+LDx, $P = 0.027$) and entry into L in the LD box test (control vs CORT, $P = 0.033$). Corticosterone induced anxiety-like behavior in the LD box test and depression-like behavior in the novelty suppressed feeding test (Fig. 5C and E, respectively); whereas, the long photoperiod did not induce any significant change in behavioral tests (Fig. 5B–E), but markedly increased

(A) LD12:12

12:12
12:12
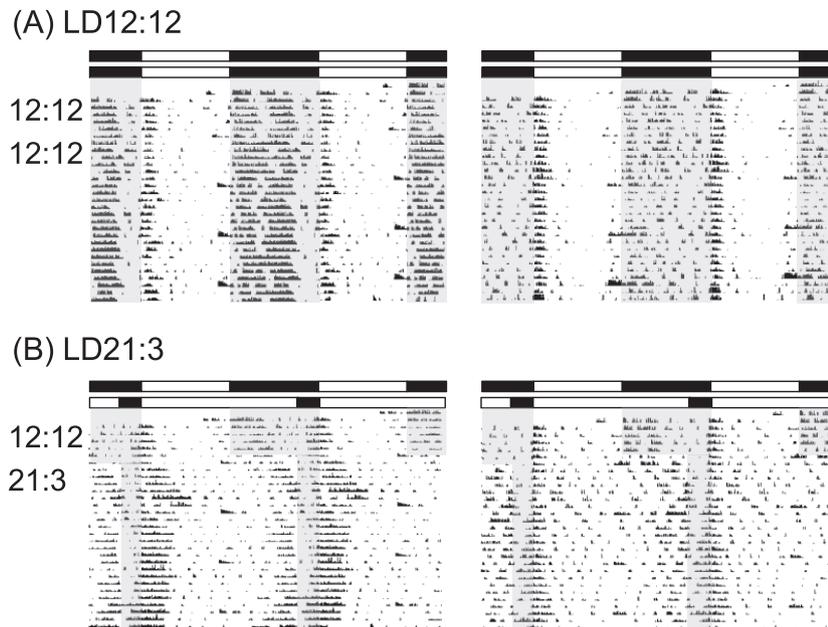
(B) LD21:3

12:12
21:3

Fig. 4 Activity rhythms of mice during long photoperiods. Representative double-plotted actograms of mice in LD12 : 12 and LD21 : 3 are shown. The mice were maintained in a normal photoperiod (LD12 : 12) for 5 days and then in a normal (A) or long (LD21 : 3, B) photoperiod. Black columns on the row represent an activity count in a 1-min bin. Each row represents a 2-day period of activity, and the graph overall represents activity during a total of 4 weeks. Horizontal white and black bars at the top represent light and dark periods, respectively, and shaded gray areas in the actogram represent dark periods.
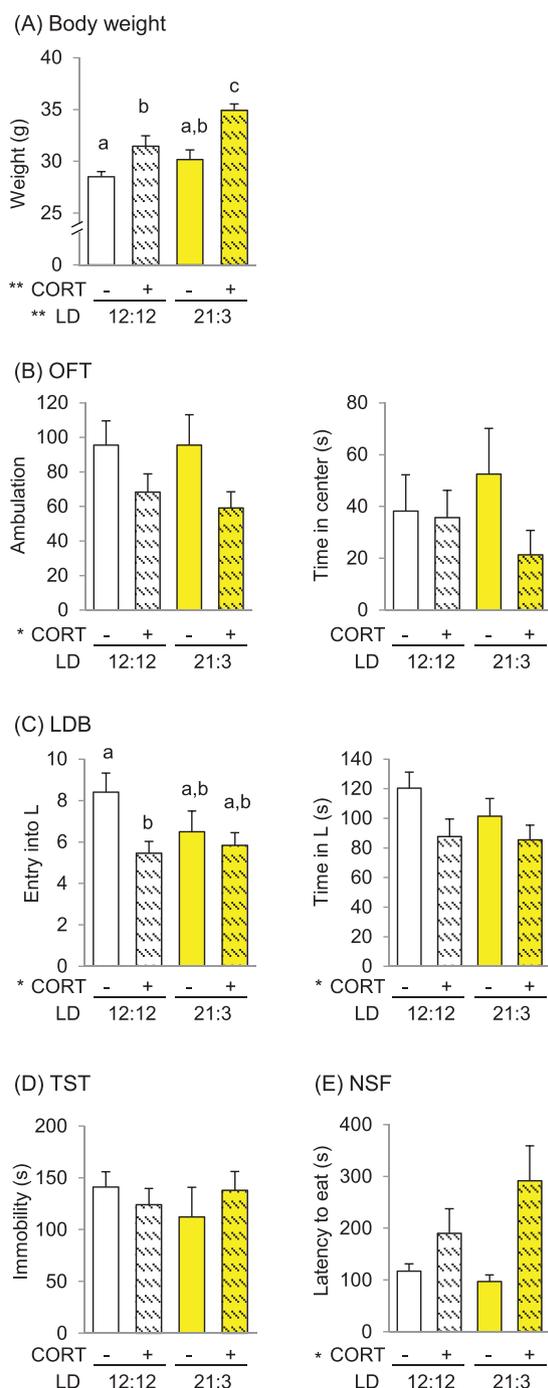
body weight (Fig. 5A).

The long photoperiod showed significant effect only on the body weight. Although the long photoperiod alone slightly increased the body weight, the difference against control was small, suggesting that the long photoperiod alone had little effect on the body weight gain. Corticosterone increased body weight in the normal LD conditions (LD12 : 12), and further increased it in the long photoperiod (LD21 : 3). Although the interaction effect was not significant in body weight by two-way ANOVA (F = 1.190, P = 0.283), the long photoperiod seemed to reinforce the effect of corticosterone on weight gain.

DISCUSSION

In this study, we analyzed the effects of aberrant LD conditions on depression and other symptoms, and revealed that short day and long day conditions have different effects on corticosterone-induced behavioral changes in mice. Short photoperiods worsened the depression-like symptoms of corticosterone-treated mice. On the other hand, long photoperiods showed no significant effects on depression-like symptoms, but enhanced weight gain in corticosterone-treated mice. The short and long photoperiods enhanced the effects of corticosterone in different ways. Short

photoperiods could affect mood, whereas long photoperiods could affect weight control.

The photoperiodic change alone had little effect on body weight and behaviors in the present study. We considered that the effect of LD disruption in the present study was not so strong as to initiate physical and/or psychological symptoms, but was sufficient to exacerbate the symptoms induced by other factors such as corticosterone treatment. Recently, similar exacerbating effects of LD disruption have been reported in several disease models. A short photoperiod increased the susceptibility of rats to chronic mild stress that induced depression (33). Constant light exacerbated the symptoms of schizophrenia in mutant mice that had a loss-of-function mutation in the schizophrenia risk gene (4). Chronic phase shifts and constant light accelerated the development of diabetes in diabetes-prone rats (14). LD shifting for 8 weeks promoted alcohol-induced colorectal cancer (5). Chronic LD shifting exacerbated dextran sodium sulfate-induced colitis (25). In these reports, alteration of LD conditions alone had little effect on the induction of disease-like symptoms, but greatly exacerbated the symptoms induced by other factors. Circadian disruption could induce alterations in neuronal, hormonal, and inflammatory systems such as serotonin, dopamine, melatonin, corticoste-

(A) Body weight

(B) OFT

(C) LDB

(D) TST   (E) NSF

Fig. 5 Effects of corticosterone and a long photoperiod on body weight and behavior in mice. Mice were chronically treated with corticosterone or vehicle in a normal (LD12 : 12) or long (LD21 : 3) photoperiod. On the 7th week, their body weight (A) and behaviors in the open field test (OFT; B), LD box test (LDB; C), tail suspension test (TST; D), and novelty suppressed feeding test (NSF; E) were analyzed. Values are presented as means ± SEM ($n = 6$–12). *$P < 0.05$, **$P < 0.01$ in the main effect, †$P < 0.05$ in the interaction effect of corticosterone and aberrant LD conditions by two-way ANOVA. The different letters (a, b, c) indicate a significant difference ($P < 0.05$) by Tukey's test.

roids, and inflammatory cytokines (6, 9, 14, 15). These changes induced by LD disruption might weaken the homeostatic functions of biological systems and might increase vulnerability to other disease-inducing factors.

Recently, Otsuka *et al.* reported that a short photoperiod induced depression-like symptoms in C57BL/6J mice (23). Their LD conditions (LD8 : 16 for 3 weeks) differed from ours (LD6 : 18 for 6 weeks). Although the mice in our study were exposed to a more extreme photoperiod for a longer duration, we did not detect depression-like symptoms in the behavioral tests. One of the reasons for this inconsistency may be the differences in experimental settings. First, Otsuka *et al.* used C57BL/6J mice, whereas we used C57BL/6N mice. Despite their genetic similarity, C57BL/6J and C57BL/6N have some phenotypic differences including circadian rhythm and depression-like behavior (3, 27). This might cause the difference in the response to a short photoperiod. Second, Otsuka *et al.* compared mice in a short photoperiod (LD8 : 16) and those in a long photoperiod (LD16 : 8). We used mice in an intermediate photoperiod (LD12 : 12) as control. Since the long photoperiod may exert antidepressant effects in mice (20), the comparison with a long photoperiod might increase the sensitivity of detecting depression-inducing effects of a short photoperiod.

The effect of a short photoperiod on depression has been investigated to develop animal models of SAD (seasonal affective disorder). Melatonin might play an important role in sensing the length of a photoperiod and in the induction of SAD (32). Since commonly used laboratory mice including C57BL/6 are melatonin-deficient, these mice were thought to be insensitive to short photoperiods and to be inappropriate as a model of SAD (11, 32). In the present study, we revealed that a short photoperiod in combination with corticosterone treatment induced depression-like symptoms in the novelty suppressed feeding test. These results confirm the finding by Otsuka *et al.* that C57BL/6 mice could be useful for the analysis of SAD (23). The CORT+short photoperiod model may be useful for investigating the effect of LD conditions on depression and SAD in commonly used laboratory mice.

The effects of a long photoperiod on mood vary from report to report. In one study, a long photoperiod (LD14 : 10) for 30 days provided an antidepressant effect in mice (20). In another report, a long photoperiod (LD19 : 5) for 1 week induced depression and anxiety in mice (8). Constant light (LL, LD24 : 0) or dim light at night also induced depres-

sion in mice (12, 28). We suspect that the length of the light period might contribute to this difference. Mild long-day stimuli might provide ameliorative effects on mood, but the extreme long-day stimuli might disrupt the circadian system and exert toxic effects. In the present study, we used extreme long-day stimuli (LD21 : 3 for 6 weeks), and detected neither depression-inducing nor antidepressant effects of a long photoperiod (LD21 : 3) even in combination with corticosterone. However, CORT+LD21 : 3 mice showed a large increase in latency in the novelty suppressed feeding test, although the effect was not significant (Fig. 5). In that experiment, some CORT+LD21 : 3 mice showed a long latency in the test, but others showed a short latency. We suspect that individual mice vary significantly in their susceptibility to LD disruption. An extremely long photoperiod might exacerbate depression-like symptoms in vulnerable mice, but the same stimuli might not induce toxic effects in tolerant mice.

Although the long photoperiod showed no obvious effect on mood, it did have a large effect on body weight. We revealed that the long photoperiod enhanced corticosterone-induced weight gain (Fig. 5A). The effect of corticosterone or a long photoperiod on body weight has been reported previously. Chronic corticosterone treatment attenuates hypothalamic-pituitary-adrenal axis function and increases food consumption, which may result in the increase in body weight (8). Mice maintained in a long photoperiod after birth use the glycolytic pathway rather than fatty acid oxidation for energy expenditure and show enhanced weight gain (31). This effect was limited to infant mice. Mice over 4 weeks of age did not show such an effect after exposure to a long photoperiod for several weeks (31). Our result in Fig. 5 confirms that a long photoperiod alone had little effect on body weight in adult mice. Furthermore, we revealed that a long photoperiod could enhance corticosterone-induced weight gain. Chronic exposure to a long photoperiod might affect energy metabolism not only in infants but also in adults. The effect might be so small in adults that weight gain could be detectable only when combined with another factor (corticosterone administration).

Several reports indicated that mice in aberrant LD conditions (light at night) or under restricted feeding showed increased body mass by increasing their food intake in the light period (1, 13). In the present study, mice in LD21 : 3 showed increased locomotor activity in the light period (Fig. 4). Although we did not measure food intake, these mice might eat large amounts of food in the light period, which might

contribute to the increased body weight. Although the precise mechanism underlying the interaction between corticosterone treatment and a long photoperiod remains to be clarified, aberrant LD conditions might be an important risk factor for stress-induced obesity in adults.

In conclusion, this study revealed that LD disruption with a short or long photoperiod could be an exacerbating factor for various symptoms, and that the short and long photoperiods exert different effects. A short photoperiod affects mood, whereas a long photoperiod affects weight control. The effect of aberrant LD conditions in the present study might be so small that it alone could not induce obvious symptoms, but might be sufficient to exacerbate the symptoms induced by other factors. Since people are exposed to various stresses and risk factors, LD disruption could have a large impact on the development and prevention of diseases in those individuals. Mouse with CORT+aberrant LD might be a useful model for investigating the effects of LD conditions on depression, obesity, and other symptoms in such stressful circumstances. The interactions among photoperiod, corticosterone, clock system, mood system, and energy metabolism should be further studied to clarify the mechanisms underlying the phenomena observed in this study.

CONFLICTS OF INTEREST

The authors have no competing interests to declare.

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