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Original Article

The effect of photoperiodic stress on anxiety-like behaviors, learning, memory, locomotor activity and memory consolidation in rats

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ABSTRACT

Introduction: Light-dark cycles regulate the body's physiological activity; hence, marked changes in these cycles could lead to conditions with impaired brain functions and disrupted moods (e.g., stress). Therefore, this study compared the impact of stress due to various photoperiodic durations on anxiety-like behavior, learning, memory, locomotor activity and memory consolidation in rats.

Methods: Thirty-five male rats were divided into five groups with different light(L)-dark(D) cycles: L20/D4, L16/D8, L12/D12 (control), L8/D16 and L4/D20 groups. After14 days, the elevated plus-maze (EPM) and passive avoidance (PA) tests were performed to assess the anxiety-like behaviors and brain functions.

Results: The percentage of spent time, number of entries to the open arm of the EPM test and the entrance latency to the dark room of the PA test decreased significantly in the L20/D4 and L4/D20 groups; however, the reduction of latency to enter the dark room was particularly significant in the L20/D4 group. In addition, there were significant differences between the initial latency and latency after one day (as learning) in all experimental groups. The total dark stay time increased significantly in different photoperiods.

Conclusion: An abnormal light-dark length could disrupt certain brain functions, such as learning, memory, locomotor activity, memory consolidation and anxiety-like behavioral responses at different levels in a time-independent manner. The light-dark length (both minimum and especially the maximum day length) led to increased learning impairment and memory deficits, as well as worsened anxiety-like behaviors. The memory consolidation was also disrupted with various photoperiods.

Keywords:
Photoperiod
Learning
Memory
Anxiety
Rat

Introduction

The light-dark cycles regulate the circadian rhythms of different physiological processes in mammals (Atger et al., 2017). The external environmental factors, such as light-dark cycles, supply the essential information to control the physiological systems in the body (Lee and Wisor 2021). Also, the changes in the light-dark cycles involve the onset of various nervous system deficits, including cognitive function disorders (learning and memory) and mental health issues (Logan and McClung

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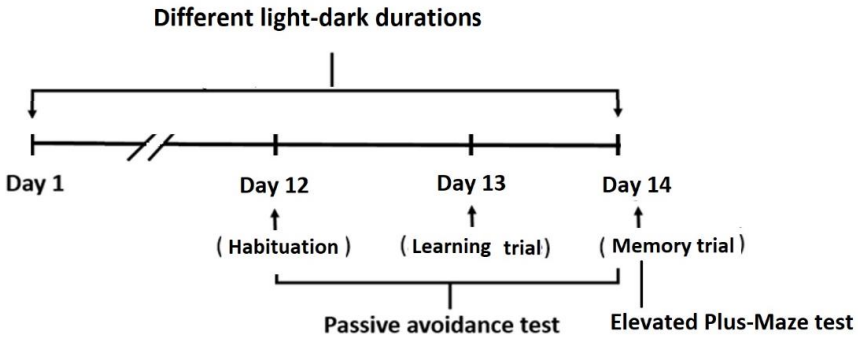

FIGURE 1. Field-Emission SEM image of E2 formulation composed of different weight ratios of surfactants (span 60: tween 60): cholesterol

2019). Recent studies have considered all internal or external environmental challenges as stress (Hadad-Ophir et al., 2014; Radahmadi et al., 2017; Zhang 2022). However, the modern lifestyle inevitably changes the length of light-dark cycles, putting many individuals under stressful conditions in such a way that a large population is (either willingly and voluntarily, or unwillingly and compulsorily) exposed to various photoperiods (Takahashi 2014). These changes could be due to different lifestyles (Stothard et al., 2017; Youngstedt et al., 2019), climate, social position (Farhud and Aryan 2018; Leach et al., 2013) and some illnesses, such as Alzheimer's disease (Phan and Malkani 2019), depression (Ma and Li 2017), usage of sedatives (Ruan et al., 2021), antipsychotic drugs (Lunsford-Avery et al., 2017), and antidepressants (Bellivier et al., 2015). Also, different light-dark lengths are observed in some occupations (e.g., flight control towers, hospital treatment staff, security centers, etc.) where a high-performance brain is required to be capable of precision, focus and conscious awareness. Therefore, the changes in light-dark length would influence cognitive functions, such as learning, memory, anxiety-like behaviors and mental health (Kaliyaperumal et al., 2017). It is reported that long days decreased object recognition (Barnes et al., 2017), also, it reduced the spatial working memory in rats but did not affect their visual working memory (Arziqni and Hadi 2021). Moreover, different light-dark lengths impair spatial memory and retrieve memory information (Zelinski et al., 2014). Another study has indicated that shorter days, compared with the longer ones, had reduced the hippocampal volume. Short days also disrupt spatial learning and memory compared with long days although they did not affect other memory types (Pyter et al., 2005a). Moreover, manipulating the dark-light cycle leads to depressive or anxiety-like behaviors in rodents (Beauvalet et al., 2019). Hence, exposure to an unnatural light-dark cycle could affect the mood state (Fonken et al., 2009). Furthermore, there is information on the impact of light-dark rhythm changes on brain functions although there is no comparative research on the definitive effectiveness of various photoperiods with different light-dark lengths on various brain functions and other psychological aspects. Therefore, this study compared the impact of stress due to various photoperiodic durations on anxiety-like behavior, learning, memory, locomotor activity and memory consolidation in rats.

Material and methods

Experimental animals

Thirty-five male Wistar rats (with an initial weight between 200 and 250g) were used in this study. All rats were kept in standard humidity (55±5%) and temperature (23±2°C) conditions with *ad libitum* food and water. The rats were allowed to be acclimatized to the animal house for two weeks before the experiments (Subhadeep et al., 2020). The subsequent experiments for each group also lasted for 14 days. The animals were randomly assigned to five groups (n=7 each) with different light-dark duration: the control group with a 12:12 h light-dark cycle (L12/D12), as well as 20:4 h (L20/D4), 16:8 h (L16/D8), 8:16 h (L8/D16) and 4:20 h (L4/D20) light-dark cycle groups.

Finally, the behavioral evaluations, including the elevated plus-maze (EPM) and passive avoidance (PA) tests were performed on day 14 after placing the rats in different light-dark conditions (Figure 1).

All the experiments were approved by the Research and Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1400.333).

Behavioral paradigms

EPM test

The EPM test is commonly performed to evaluate anxiety-like behaviors in rodents (Knight et al., 2021). In this study, the EPM apparatus had two open (50×10×0.5cm) and two closed (50×10×30cm) arms, extending from a common central platform (10×10cm). The EPM was elevated 70cm above the floor. On day 14, the animals were individually placed in the maze center, and their behavioral responses were recorded for 300s. After each session, the maze was wiped and cleaned (with ethanol 70%). Finally, the animals were returned to their cages. The EPM scoring included the percentages of open arm time spent (%OAT) and entries (%OAE). To evaluate anxiety, the following formulae were used in the EPM test: [%OAE=(the number of open arm entries/the number of open+closed arm entries)×100] and [%OAT=(the time spent in the open arms/the time spent in the open+-closed arms)×100] (Hafez and Gad 2018). Also, the total arm entries during the trial (300s) were considered as the locomotor activity measure in the EPM test (Boerngen-Lacerda and Souza-Formigoni 2000).

PA test

In this study, the PA test was used as a behavioral task to measure learning, memory and memory consolidation as different aspects of brain functions. The PA apparatus (64×25×35cm) was divided into two rooms of the same size with similar grid floors, which were separated by a sliding guillotine door. This protocol was performed based on a previous study (Kalantarzadeh et al., 2020). On day 12 of the experiment, each animal was located in the PA apparatus for 300s for habituation. A single learning trial was performed on day 13 by delivering a single electrical foot shock (0.5mA, 2s) through grid floors. Subsequently, the PA test evaluated the memory on the next day (day 14). The initial latency to enter the dark room was recorded before inducing the electrical shock. Moreover, in the memory trial, the latency after a day was measured with the dark room entrance delay (up to a maximum duration of 300s). The total dark stay (DS) time was recorded as the storage of new information and/or memory consolidation (Kalantarzadeh et al., 2020).

Statistical analysis

To assess the normal sampling distribution, the Kolmogorov–Smirnov (K-S) test was employed. Also, the statistical analysis with the analysis of variance (ANOVA) test was followed by Least Significant Difference (LSD) post-hoc test for multiple groups. Moreover, using the paired-sample t-test, the initial latency and latency after a day (within-group) were compared. All data were estimated as mean±SEM and the *P*-value less than 0.05 was considered statistically significant. All calculations were done by IBM SPSS Statistics (v. 26).

Results

Assessing the anxiety-like behaviors and locomotor activity

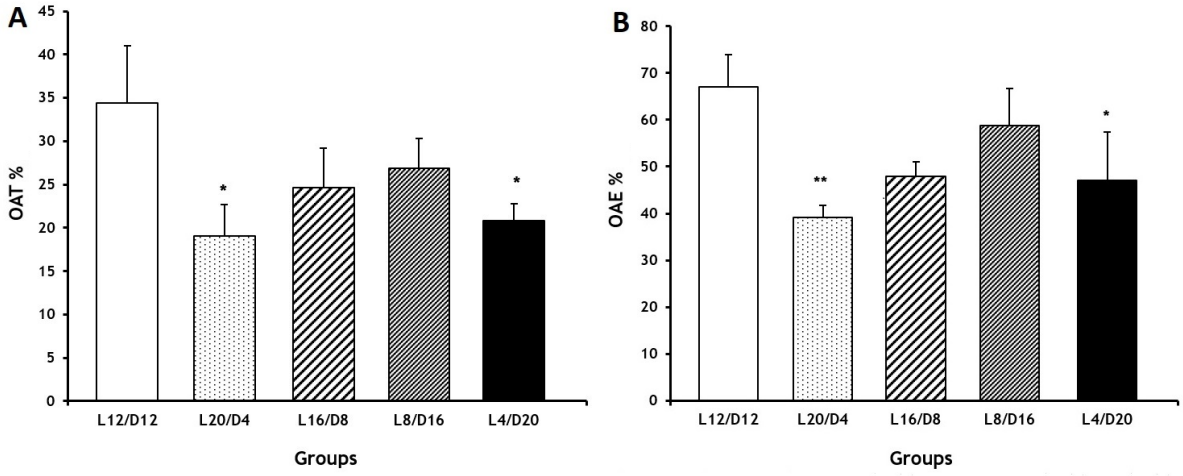

FIGURE 2. F(A) The percentage of open arm time spent (%OAT) and (B) the percentage of open arm entries (%OAE) in the EPM for all experimental groups (n=7). Results are expressed as mean±SEM (ANOVA test, LSD post-hoc test);$^{*}P<0.05$;$^{**}P<0.01$ compared with the L12/D12 (Control) group. L20/D4: 20-04 h light-dark cycle, L16 /D8: 16-04 h light-dark cycle, L12/D12: 12-12h light-dark cycle (Control group), L8/D16: 8-16h light-dark cycle, L4/D20: 4-20h light-dark cycle.

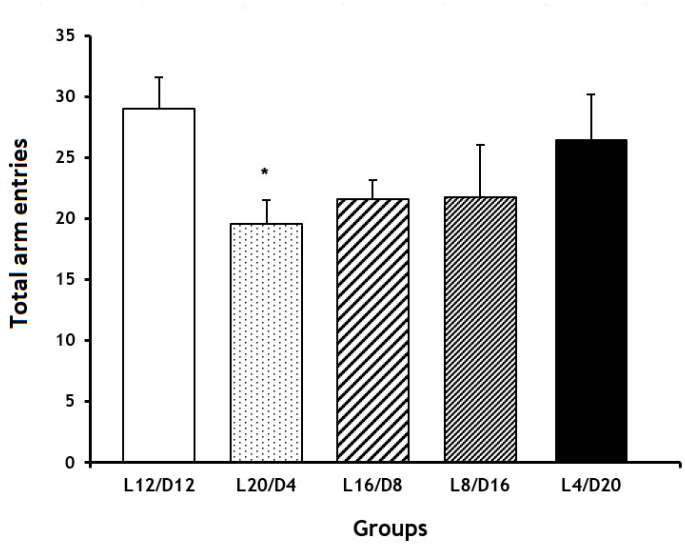

FIGURE 3. Total arm in the EPM apparatus for all groups (n=7). Results are expressed as mean±SEM (ANOVA test, LSD post-hoc test); $^{*}P<0.05$ compared with the L12/D12 (Control) group. L20/D4: 20-04 h light-dark cycle, L16 /D8: 16-04 h light-dark cycle, L12/D12: 12-12h light-dark cycle (Control group), L8/D16: 8-16h light-dark cycle, L4/D20: 4-20h light-dark cycle.

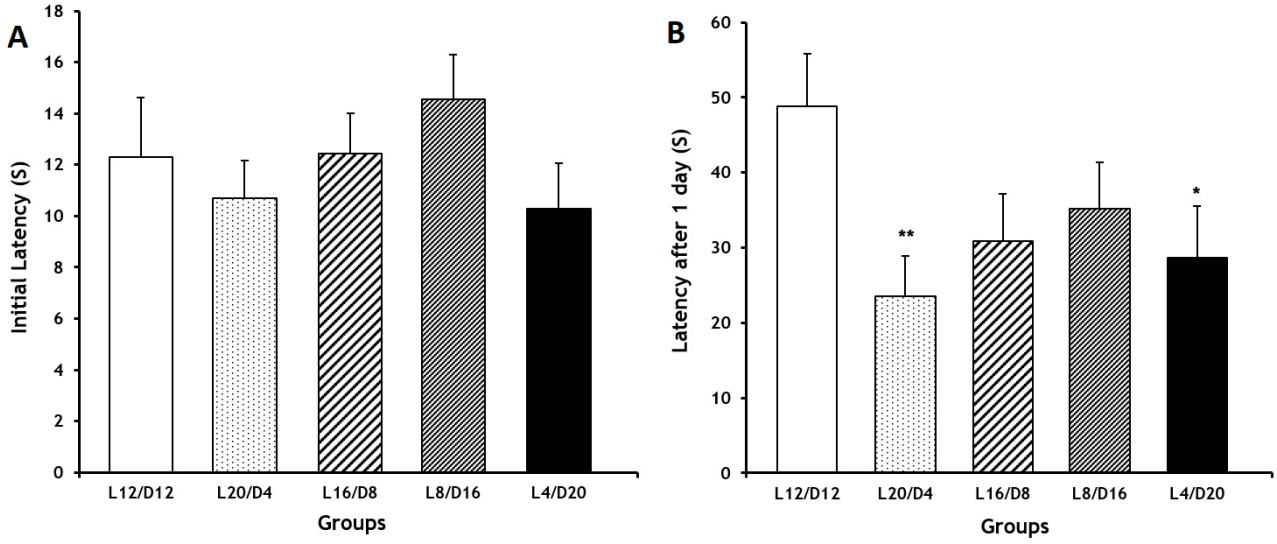

FIGURE 4. (A) The initial latency to enter the dark room of the PA apparatus before receiving foot-shock (B) Latency to enter the dark room of the PA apparatus one-day after receiving the foot shock for all experimental groups (n=7). Results are expressed as mean±SEM (ANOVA test, LSD post-hoc test); $^{*}P<0.05$; $^{**}P<0.01$ compared with the L12/D12 (Control) group. L20/D4: 20-04 h light-dark cycle, L16 /D8: 16-04 h light-dark cycle, L12/D12: 12-12h light-dark cycle (Control group), L8/D16: 8-16h light-dark cycle, L4/D20: 4-20h light-dark cycle.

In the EPM test, the ANOVA assigned different significant levels for variables as %OAT [F(4, 30)=1.952, $P>0.05$], %OAE [F(4, 30)=2.593, $P<0.05$] and total arm entries [F(4, 30)=1.677, $P>0.05$]. According to the EPM test, the L20/D4 and L4/D20 groups showed significant reductions of %OAT ($P<0.05$, both; Figure 2A) and %OAE ($P<0.01$ and $p<0.05$, respectively; Figure 2B) in comparison with the control group. Also, the total EPM entries decreased significantly ($P<0.05$) in the L20/D4 group compared with the control group (Figure 3).

Assessing learning and memory

In the PA test, the ANOVA assigned different significant levels to variables as initial latency [F(4, 30)=0.895, $P>0.05$], latency after a day [F(4, 30)=2.257, $P>0.05$] and total DS time [F(4, 30)=6.472, $P<0.01$]. In Figure 4, the initial latency and the latency after one day in the PA test are shown. There were no significant differences in the initial latency of all groups with different light-dark cycles (Figure 4A). However, the latency after one day significantly decreased in the L20/D4 and L4/D20 groups ($P<0.01$ and $P<0.05$, respectively) in compari-

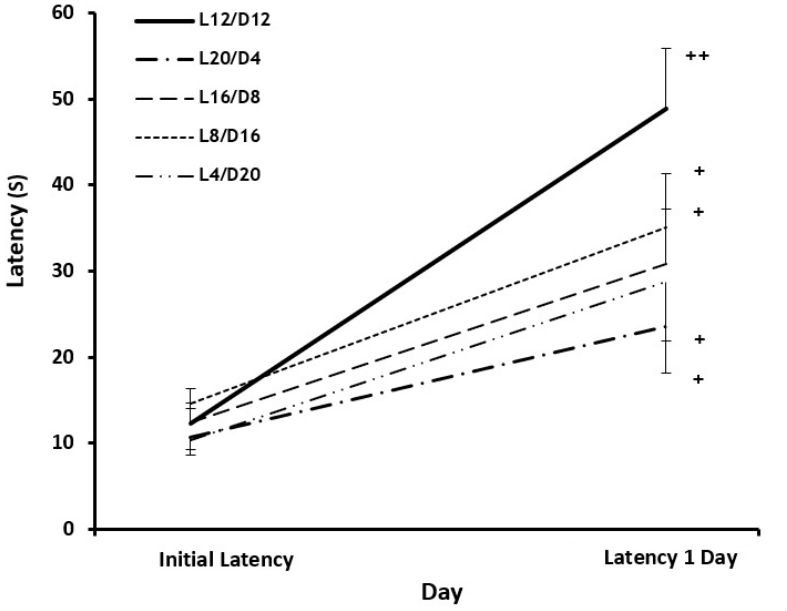

FIGURE 5. Initial latency and latency after 1 day to entrance into the dark room of the passive avoidance appa-ratus before and after the foot shock (within-group) (n= 7). Results are expressed as mean±SEM (Paired sample t-test);^{+}P<0.05 and ^{++}P<0.01 initial latency relative to the latency after one day. L20/D4: 20-04 h light-dark cycle, L16 /D8: 16-04 h light-dark cycle, L12/D12: 12-12h light-dark cycle (Control group), L8/D16: 8-16h light-dark cycle, L4/D20: 4-20h light-dark cycle.

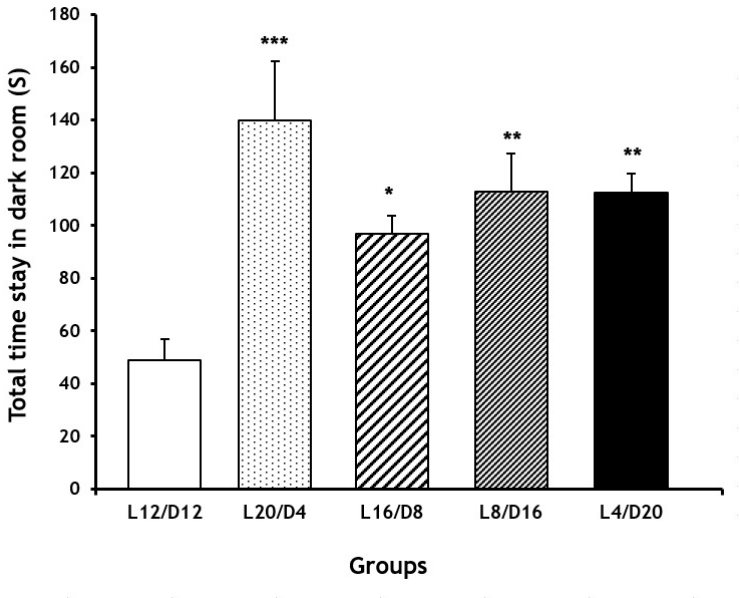

FIGURE 6. Total stay time in dark room of the passive avoidance apparatus 1 day after receiving the foot shock for all groups (n=7). Results are expressed as mean±SEM (ANOVA test, LSD post-hoc test); $^{*}P$<0.05;$^{**}P$<0.01 and $^{***}P$<0.001 compared with the L12/D12 (Control) group. L20/D4: 20-04 h light-dark cycle, L16 /D8: 16-04 h light-dark cycle, L12/D12: 12-12h light-dark cycle (Control group), L8/D16: 8-16h light-dark cycle, L4/D20: 4-20h light-dark cycle.

son with the control group (Figure 4B).

Using a paired sample t-test, the values of initial latency and latency after one day were analyzed to evaluate the within-group latency changes. There were significant differences between the initial latency and latency after one day in experimental groups. As observed in Figure 5, in the L12/D12 [t(6)=-5.200, p<0.01], L20/D4 [t(6)=-2.898, P<0.05], L16/D8 [t(6)=-2.923, P<0.05], L8/D16 [t(6)=-3.361, P<0.05] and L4/D20 [t(6)=-2.466, P<0.05] groups, learning occurred at various levels. However, the lowest level was associated with the L20/D4 group.

According to Figure 5, the DS time increased significantly ($P<0.001$, $P<0.05$, $P<0.05$ and $P<0.01$, respectively) in the L20/D4, L16/D8, L8/D16 and L4/D20 groups in comparison with the control group. Therefore, different photoperiods severely disrupted the memory consolidation in all experimental groups (Figure 6).

Discussion

The effect of photoperiodic stress was investigated on anxiety-like behaviors and different aspects of brain functions (learning, memory, locomotor activity and memory consolidation) in rats. Previous studies have shown that different light-dark periods (light lengths higher and shorter than normal conditions) may cause various types of disorders in the nervous system and secretory endocrine glands (Leach et al., 2013; Russell and Lightman 2019; Gu et al., 2019). However, no comparison was made between the effects of different lengths of the light-dark cycles on multiple brain functions previously.

Based on the EPM findings, anxiety-like behaviors were increased in L4/D20 and especially in the L20/D4 group. Therefore, the risk-taking behaviors decreased in these two groups. It seems that the minimum and maximum light lengths induced psychological stress. In the present study, the highest and lowest light durations increased anxiety-like behaviors. In some studies, lengthy periods of exposure to light increased anxiety and depressive behavioral responses (Barnes et al., 2017; Fonken et al., 2009), probably, due to the increased anxiety levels in longer light durations. By contrast, another study found that increasing the length of the light period reduced anxiety-like behaviors and social cognition as those were improved by long day durations (Subhadeep et al., 2020). It was also reported that abnormal light-dark cycles could disrupt the normal biological rhythms of glucocorticoids and melatonin secretion. Therefore irregular light-dark cycles could alter their levels in the serum (Arziqni and Hadi 2021). Since the levels of these hormones rhythmically change throughout the day-night cycle, a disrupted light-dark rhythm could lead to neurological and psychological diseases (Tahara et al., 2016; Landgraf et al., 2014) For instance, memory deficit, anxiety, depression-like behaviors, aggression and other mood disorders (Hou et al., 2022; McEwen 2005; Silva et al., 2010), for which different mechanisms are suggested as well. Some of these mechanisms include the changes in hormonal levels (e.g., glucocorticoids and melatonin) (Klyubin et al., 2022; Thangwong et al., 2022), neurotransmitters (Hosseini-Sharifabad et al., 2021), brain-derived neurotrophic factor (BDNF) (Lee et al., 2022), oxidative stress (Lu et al., 2022), reduced glutamate receptors (Hou et al., 2022), and morphological changes, which might be present in specific brain areas, such as the changes in dendritic and spine density, brain size, hippocampal volume, soma size (Walton et al., 2011a; Pyter et al., 2005b; Breuner and Wingfield 2000; Boonstra and McColl 2000; Workman et al., 2011), loss of neurons and astrocytes, as well as the synaptic damage in the surviving pyramidal cells cells (Hosseini-Sharifabad et al., 2021; Tamminga et al., 2012; Hou et al., 2022). Similar to the impact of light duration on the nervous system, exogenous melatonin administration is also implicated in damage prevention in the nervous system (Valdés-Tovar et al., 2018). Notably, the emotional and behavioral responses to the light periods might not have been related to adrenal gland activities alone (Fonken et al., 2009). Moreover, the locomotor activity in the EPM only decreased in the L20/D4 group. Therefore, stress and anxiety due to longer light periods seem to have reduced locomotor activity. Correspondingly, reduced locomotor activity by stress (Sestakova et al., 2013), increased locomotor activity caused by social isolation stress and in response to novel situations for rats were reported in other studies (Weiss et al., 2000). These paradoxical findings could be related to different factors like gender, age, species, length of experimental period and nature of the subject, stress duration and the behavioral task (Ranjbar et al., 2016).

According to the PA findings, learning occurred at different levels in all groups, where the lowest learning level was seen in the L20/D4 group with the highest light duration. However, there are paradoxical reports regarding the learning level in relation to different light lengths. A study demonstrated that longer light periods caused learning disabilities (López-Olmeda et al., 2021). However, in other studies shorter light periods impaired spatial learning (Pyter et al., 2005a; Walton et al., 2011b). Also, chronic exposure to low light increased depressive behaviors associated with learning and memory impairments (Emmer et al., 2018). Also, prolonged exposure to light or even resting in light

conditions could impair learning (López-Olmeda et al., 2021). In support of this view, previous studies have reported that stress could lead to impaired physiological responses and accelerated damage to cognitive activities like learning, and memory (Zoeram et al., 2019; Do Nascimento et al., 2019; Ouanes and Popp 2019). Based on the EPM findings in this study, photoperiodic stress impaired learning in irregular light-dark cycles. Another study demonstrated that melanopsins (photopigments) were activated even at low light intensities. Therefore, the externally-imposed environmental light could cause disturbance in circadian rhythm and learning (Emmer et al., 2018).

Another finding in this study demonstrates the occurrence of memory impairment in the L4/D20 and particularly L20/D4 groups (as the minimum and maximum light lengths, respectively). Therefore, memory changes seem to have been time-independent. Conversely, memory consolidation was impaired in all experimental groups with different photoperiods. In line with the present study, a report has shown that long periods of light exposure significantly reduced spatial working memory but did not affect the visual working memory in rodents rodents (Arziqni and Hadi 2021). Also, certain neural activities were reduced significantly in the constant and prolonged light duration (Arziqni and Hadi 2021). Nonetheless, a short light period (compared with the long one) impaired learning and long-term memory; however, it did not affect sensory differentiation or other types of memory (Pyter et al., 2005a). It was also reported that exposure to constant and long-term darkness reduced the complex structure and morphology in the hippocampal cornu ammonis 1 (CA1) and dentate gyrus (Patki et al., 2013). Subhadee et al. (2021) reported that a short light period increased the expression of hippocampal glucocorticoid receptors, activity-regulated cytoskeleton-associated protein, and neurogenesis. Thus, the role of short light periods in cognitive recovery was implicated in a neurodegenerative model (Subhadeep et al., 2021). Light periods could impair hippocampal-dependent learning/spatial memory and reduce the CA1 dendritic growth density, as well as the hippocampal BDNF expression (Soler et al., 2019). Moreover, changing the light-dark length might decrease synaptic plasticity and cognitive performance (Dastgerdi et al., 2020; Yang et al., 2007). As such, long-term exposure to variable light periods reduced the number of neurons and glutamate receptors (Hou et al., 2022). In brief, previous studies have shown that different lengths of the light-dark periods may impair some brain functions. That is because both long- and short-length rhythms could influence biological systems. Since the exact photoperiodic rhythm (long or short days), affecting memory processing and anxiety was not indicated in previous literature, the alterations of brain functions by light-dark lengths remain paradoxical. In addition, there were no coherent reports on the effect of different lengths of the light-dark periods on brain functions under the same laboratory conditions. Hence, as a research novelty, the present study investigated the effects of different photoperiods (with regularly increasing four-hour intervals) on memory changes and induction of anxiety under the same laboratory conditions. Overall, results of this study showed that the impairment of brain functions did not have any direct and regular relationship with the light length.

Conclusion

In summary, an irregular trend of light-dark length could disrupt some brain functions, such as learning, memory consolidation, memory, locomotor activity and anxiety-like behavioral responses at different levels in a time-independent manner. The minimum and maximum lengths of the light-dark period caused the highest learning and memory deficits, as well as anxiety-like behaviors. Also, memory consolidation was disrupted in various photoperiods. However, further molecular, electrophysiological and biochemical research is required to trace and clarify the involved mechanism(s).

Conflict of interest

The authors declare no conflict of interest.

Acknowledgment

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