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Research article

Light deprivation produces a sexual dimorphic effect on neural excitability and depression-like behavior in mice

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HIGHLIGHTS

- Light deprivation produces a sexual dimorphic effect on depression-like behavior.
- Light deprivation induces more severe depressive-like symptoms in female mice.
- Light deprivation leads to weaker locomotor activity in female depressive-like mice.
- Light deprivation leads to lower excitability of L5PCs in female depressive-like mice.
- Lower excitability of L5PCs may correlate with more severe depressive-like symptoms.

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ABSTRACT

Light sensory experience plays a crucial role in the regulation of mood, and light deficiency is considered as one important factor potentially leading to depression. Women are twice as likely as men to suffer from depression. However, the physiological mechanism underlying sex differences in the prevalence, incidence and morbidity risk of depression is still poorly understood. The potential causal relationship between sex dimorphic behavioral deficits and altered intrinsic electrophysiological properties of Layer V pyramidal cells (L5PCs) in the motor cortex was investigated using a mouse model with depression-like behavior that was induced by light deprivation. The depression-like behavior was characterized by increased immobility and decreased activity in the forced swimming test and tail suspension test. Compared with male depressive-like mice, light deprivation (LD) induced longer immobile behavior while shorter active behavior in female depressive-like mice, indicating that LD produces a sexual dimorphic effect on depression-like behavior with more severe depressive-like symptoms in females. LD induced lower locomotor activity in female depressive-like mice as evidenced by the significant decrease in pole-climbing and swimming during the anti-static fatigue test and exhaustive swimming test correspondingly. LD also significantly decreased the intrinsic excitability of L5PCs in female depressive-like mice, which may explain the reduced active behavior and locomotor activity of female mice. Collectively, it indicates that LD produces a sexual dimorphic effect on the depression-like behavior, locomotor activity and neural excitability in mice, and may suggest a causal relationship between the more severe depressive conditions and decreased neural excitability of L5PCs in female mice. These divergent findings from male and female depressive-like mice may provide one potential route to the physiological mechanism underlying sex differences in the prevalence of depression at a level of single neurons.

1. Introduction

Light plays a crucial role in the regulation of mood, and light deficiency is considered as one important factor potentially leading to depression. The seasonal affective disorder commonly defined as a seasonal pattern of major depression disorder occurs at a high frequency in high latitudes where light exposure is limited [1]. On the other hand, the bright light therapy is an effective

Abbreviations: AP, action potential; CLIMB, climbing; FST, forced swimming test; IMMOB, immobility; L5PCs, Layer V pyramidal cells; PAW, pawing; SWIM, swimming; TST, tail suspension test.

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antidepressant treatment for humans, which significantly relieves depression symptoms [2–4]. This suggests that appropriate light exposure is one crucial factor for preventing humans from being in depressive condition. Interestingly, animal studies showed that a depressive behavioral phenotype in rodents has been produced by giving either a chronic constant light [5] or the light deprivation (LD) [6–8], indicating that a normal light-dark cycle is also important for animals obtaining proper light exposure. Collectively, it implies that appropriate light exposure is vital for both animals and humans, and the disturbance of light-dark alterations may have a causal relationship with depression.

Depression is one of the most prevalent and life-threatening forms of mental illness [9]. Sex differences in the prevalence, incidence and morbidity risk of major depressive disorder have been well documented [10]. Women are twice as likely as men to suffer from depression [11] and sex differences also exist in antidepressant treatment responses [12]. Nevertheless, the physiological mechanism underlying sex differences in theses aspects is still poorly understood. The emergence of some animal models of depression makes it more convenient for uncovering the pathogenesis of depression [13]. In rat models with depressive-like symptoms, sex differences were observed in behavioral responses during the forced swimming test (FST), and the head swinging was mostly present in male rats [14]. The rats with depressive behavioral phenotypes that were induced by LD also showed a pre-existing behavioral deficit as evidenced by a significant decrease in climbing, swimming and pawing during the FST [6]. The decreased active behaviors in the FST may imply an impaired locomotor activity in depressive-like animal models. LD could well produce a depression-like behavior in rodents [6–8]. However, the physiological mechanism underlying how the LD induces sexually dimorphic behaviors acting as indicators of depression and the sexually dimorphic effect of LD on the locomotor activity of depression-like behavior mice, still remains largely unknown.

The sexually dimorphic behavioral deficit exhibited in depression-like behavior mice may correlate with the changes of neural electrophysiological properties. Pyramidal cells (PCs) in the cerebral cortex are principal excitatory neurons, forming local excitatory connections and providing cortico-cortical and cortical-subcortical projections [15,16], and Layer V (L5) as the major output layer contains the largest PCs in the cortex. Most L5 pyramidal cells (L5PCs) send axons subcortically or contralaterally to fulfill the information processing, and play important roles in neural information processing in the nervous system [17,18]. Neural excitability in the cerebral motor cortex is associated with some human neurological disorders such as epilepsy and Parkinson's disease [19,20]. Moreover, our previous study has confirmed that the abnormality of intrinsic electrophysiological properties of L5PCs in mouse motor cortex may have a causal relationship with neurological disorders [21]. Depression is a neurological disorder characterized by a state of low mood and aversion to activity. The social defeat stress mice model of depression displayed hyperactivity of dopamine neurons in the ventral tegmental area [22]. The abnormality of neuronal excitability could lead to more difficulty in processing inputs and remodeling synapses [23]. This indicates that the excitability of single neurons exerts a great influence on the synaptic plasticity. All patterns of behavior are produced by interacting nerve cells, and changes of single neural excitability may potentially contribute to behavioral deficits in depression-like behavior mice. It has been documented that electrophysiological responses of motor cortex neurons are closely related to mammalian locomotor behavior [24,25]. However, the potential causal relationship between the sex difference in behavioral deficits and altered intrinsic electrophysiological properties of L5PCs in mouse motor cortex, to our best knowledge, is unknown.

In the present study, using a mouse model with depression-like behavior that was induced by LD and the whole-cell patch clamp recording, we investigated the sexual dimorphic effect of LD on depression-like behavior and intrinsic electrophysiological properties of L5PCs in mouse motor cortex, to uncover the potential causal relationship between these two aspects. This study may provide one potential route to the physiological mechanism underlying sex differences in the prevalence of depression at a level of single neurons.

2. Materials and methods

2.1. Animals and housing

Adult ICR mice were obtained from the Laboratory Animal Unit of Wenzhou Medical University. All animal experimental procedures were approved by the Animal Care and Ethics Committee at Wenzhou Medical University (approval ID: wydw 2010-0001/0002), and followed to international guidelines on the ethical use of animals. Neonatal mice were housed either in a 12/12 h light-dark cycle (the control group) or in a complete darkness (the LD group) since birth for three weeks, and then used for studies. Mice used in the behavioral assays and electrophysiological recordings were at postnatal days 22–35 (P22-P35).

2.2. Behavioral tests

2.2.1. Forced swimming test

The forced swimming test (FST) that is commonly used to assess antidepressant activity [26], was also used for testing depression-like behavior in rodents [6]. A digital video recorded behaviors during the FST. The measurements, including the immobility (IMMOB), climbing (CLIMB), pawing (PAW), and swimming (SWIM), were scored on a video monitor from taped images by two observers blind to the experimental conditions, and the mean values obtained from the two observers were used (the same for the following behavioral tests). The criteria for evaluating these behavioral measurements were as reported previously [6].

2.2.2. Tail suspension test

The depression-like behavior of mice was also assayed using the tail suspension test (TST), which is widely used for testing "behavioral despair of mouse" [27]. The time of immobility (indicator of depression-like behavior) and activity was assessed separately. The mice were considered immobile only when they hung down passively and were completely motionless.

2.2.3. Anti-static fatigue test

The mouse was located at the end of a wire (2 m in length with a diameter of 0.5 cm) that was vertically suspended with a distance of 12 cm to the floor. The time duration from the beginning of the mouse located on the wire until the mouse fell off the wire was recorded as the pole-climbing time. The pole-climbing time, as an indicator of the static locomotor activity of mice, was obtained from a mean of three repeated pole-climbing test.

2.2.4. Exhaustive swimming test

The procedure used was as described previously [28]. The exhaustion was defined as the mouse failing to rise to the surface for breathing within 7 s [29]. The time duration from the beginning of the swimming until the exhaustion was recorded as the exhaustive swimming time. The duration of exhaustive swimming was an indicator of the dynamic locomotor activity of mice.