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Research report

The first observation of seasonal affective disorder symptoms in Rhesus macaque

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HIGHLIGHTS

- Short photoperiod led monkeys to display depression-related behaviors.
- Monkeys presented with physiological abnormalities during the short photoperiod.
- Antidepressant treatment can reverse all of the depression-related symptoms.

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ABSTRACT

Diurnal animals are a better model for seasonal affective disorder (SAD) than nocturnal ones. Previous work with diurnal rodents demonstrated that short photoperiod conditions brought about depression-like behavior. However, rodents are at a large phylogenetic distance from humans. In contrast, nonhuman primates are closely similar to humans, making them an excellent candidate for SAD model. This study made the first attempt to develop SAD in rhesus macaque (*Macaca mulatta*) and it was found that short photoperiod conditions could lead monkeys to display depressive-like huddling behavior, less spontaneous locomotion, as well as less reactive locomotion. In addition to these depression-related behavioral changes, the physiological abnormalities that occur in patients with SAD, such as weight loss, anhedonia and hypercortisolism, were also observed in those SAD monkeys. Moreover, antidepressant treatment could reverse all of the depression-related symptoms, including depressive-like huddling behavior, less spontaneous locomotion, less reactive locomotion, weight loss, anhedonia and hypercortisolism. For the first time, this study observed the SAD symptoms in rhesus macaque, which would provide an important platform for the understanding of the etiology of SAD as well as developing novel therapeutic interventions in the future.

1. Introduction

Seasonal affective disorder (SAD), also known as winter depression, is a mood disorder in which people who have normal mental health throughout most of the year, but experience depressive symptoms in the winter or autumn year after year [1]. SAD was first described in 1984 [1], and exists in DSM-V (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) as "seasonal pattern", a specifier of either unipolar or bipolar affective

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disorders [2]. As is the case with other affective disorders, SAD has been more frequently observed in females than in males [3], which can be explained by the sex differences in biochemical responses to climatic variables [4].

Patients with SAD were found to have deficits in processing visual light, develop symptoms in the absence of adequate light, and respond favorably to enhanced environmental lighting [5]. Light therapy is one of the most effective treatments for SAD, further supporting the association between SAD and light [6]. Although the mechanisms through which light affects SAD were not well understood [7], many researchers have observed the depressive-like behaviors in several species by manipulating the photoperiod [8–15]. For instance, it has been found that nocturnal rodents exhibited depressive-like behavior and anhedonia when exposed to short day lengths [13–15]. However, it is controversial whether these models provide a reasonable outward representation of SAD because there are some fundamental differences between nocturnal and diurnal mammals [16]. For example, the secretion of melatonin is concurrent with the resting phase in diurnal species, whereas in nocturnal species it is related to an increase in activity [17]. In addition to this, the administration of melatonin decreases anxiety-like behavior in nocturnal species, while in diurnal species it increases it [18]. Another major difference is the behavioral responses to light and darkness. Specifically, diurnal animals become more active in response to light and less active in response to darkness, while nocturnal ones have opposite patterns of response [19–23]. Moreover, the hypothalamus-pituitary-adrenal (HPA) axis activity starts to rise at the end of the night in diurnal mammals, whereas in nocturnal animals it occurs at the end of the day [24]. The peak of serotonin also varies greatly, with the day in nocturnal species while the night in diurnal species [25]. In view of these significant differences, it is speculated that diurnal animals are a more advantageous model for SAD than nocturnal ones.

In accordance with this speculation, several studies have indeed established the model of SAD in diurnal rodents [8–12]. These animals showed depression-related symptoms when exposed to 3 weeks or more of short photoperiod. Therefore, diurnal rodents offered better utility in investigating seasonal variations in both pathological and non-pathological processes than nocturnal ones [26].

Despite these significant advancements in rodent models of SAD, it is still a question whether the behaviors observed are unique to rodents or are shared across other diurnal species, such as nonhuman primates which are most close to humans. After all, rodents are phylogenetically distant from humans, making them differ greatly from humans in many ways, such as brain structure, life style and emotional expression [27,28]. In contrast, nonhuman primates, especially rhesus macaques, are closely similar to humans in many aspects [29–32]. Firstly, the macaques' brain structure is similar to that of humans [31]. Secondly, macaques show high similarities to humans in life style. For example, they have strict social structures, a dependence on social relationships, an ability to engage in complex cognitive processes and a range of affective expression [29,30]. Last but not least, the living environments of macaques, in contrast to that of humans, can be tightly controlled and therefore provides an easier platform for experimental manipulation [29,30]. All these suggest modeling SAD in macaques would provide an important platform for the understanding of the etiology of SAD as well as developing novel therapeutic interventions in the future. However, such research has not yet been reported.

Because of the big sex differences in SAD, the present study made the first attempt to develop SAD among female rhesus macaque (*Macaca mulatta*), to test whether short photoperiod conditions can result in depression-related symptoms, and to assess whether observed depressive symptoms can be reversed by antidepressant treatment. Our study found that short photoperiod conditions did lead monkeys to display depression-related symptoms, and all of these symptoms could be reversed by antidepressant treatment. This indicates that the rhesus macaque is an excellent model for the human SAD.

2. Methods

2.1. Animals

Eight female rhesus macaques (*Macaca mulatta*) living in the Kunming Primate Research Center of the Chinese Academy of Sciences were selected and observed in this study. These animals ranged from 11 to 14 years of age (12.63 ± 1.02 years), and were singly housed ($0{\cdot}80 \times 0.80 \times 0.80$ m) in a controlled environment (temperature: $22 \pm 1\,^{\circ}$C; humidity: $50 \pm 5\%$ RH), with initial 12 h light/12 h dark cycle (lights on at 07:00 h). All animals were given commercial monkey biscuits twice a day, and were fed with fruits and vegetables once daily. The animals had lived in their respective cages for at least three months prior to initial manipulation. All efforts were made to minimize the monkeys' suffering. For example, hair samples were taken from the back of the monkeys' neck using an electric-razor without anesthetic and no animals were sacrificed in this study. Routine veterinary care was provided throughout the experiment by professional keepers and veterinarians.

All animal procedures were approved by the National Animal Research Authority (P.R.China) and the Institutional Animal Care and Use Committee (IACUC) of Kunming Institute of Zoology, Chinese Academy of Sciences.

2.2. Experimental design

Animal behaviors, body weights, sweet solution preference, and hair cortisol levels were measured before and after photoperiod manipulation to assess the animals' baseline status and influences of short photoperiod, respectively. After that, the animals were still maintained under short photoperiod condition and treated with antidepressants. When it was over, the variables mentioned above were measured again to observe whether antidepressant treatment can improve depression-related symptoms. All manipulation and testing occurred during the light phase. Prior to photoperiod manipulation, animals were habituated to experimental procedures in order to minimize stress reactivity.

2.3. Photoperiod manipulation

After three months of acclimatization to the neutral photoperiod (12 h light/12 h dark cycle), the light length of the monkeys was changed to 5-h:19-h LD (lights on at 07:00 h). The lighting regime was set based on previous studies with diurnal rodents and it had been proved to successfully model SAD in rodents [8–11].

2.4. Antidepressant treatment

After short photoperiod treatment, the monkeys were injected intramuscularly with clomipramine hydrochloride injection (CHI, Jiangsu Nhwa Pharmaceutical Co., China) to test whether observed depression-related symptoms can be reversed by antidepressant therapy. The injection dose for depressed patients was 25 mg in the first stage, and this dose was increased by 25 mg every step until 150 mg [33]. The injection dose for monkeys can be calculated using the BSA (body surface area) method. Thus, the whole process of treatment was divided into six periods: the first period with CHI doses of 1.09 mg/kg for each monkey per day, the second period with CHI doses of 2.18 mg/kg for each monkey per day, the third