



Research report

Early adversity contributes to chronic stress induced depression-like behavior in adolescent male rhesus monkeys



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HIGHLIGHTS

- Adolescent male rhesus monkeys experiencing early adversity displayed depression-like behaviors under chronic mild stress.
- Chronic mild stress induced cortisol hypersecretion in monkeys experiencing early adversity.
- Chronic mild stress also induced weight loss in monkeys with early adversity.

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ABSTRACT

Chronic stress is an important cause for depression. However, not everyone who is exposed to chronic stress will develop depression. Our previous studies demonstrated that early adversity can cause lasting changes in adolescent rhesus monkeys, but depressive symptoms have not been observed. Compared to adults, it is still unknown that whether adolescent rhesus monkeys experiencing early adversity are more likely to develop depressive symptoms. In this study, we investigated the long term relationship between early adversity, chronic stress and adolescent depression for the first time. Eight male rhesus monkeys were reared in maternal separation (MS) or mother-reared (MR) conditions. All of them went through unpredictable chronic stress for two months at their age four. The stressors included space restriction, intimidation, long illumination and fasting. Behavioral and physiological data were collected during the experiment. The results showed that, compared with the MR group, the locomotor activity of MS group was significantly decreased after one month of chronic stress while huddling up and stereotypical behaviors were significantly increased. Moreover, this trend continued and even worsened at the second month. Significantly higher hair cortisol levels and lower body weight were observed in MS group after two months of stress. These results indicate that early adversity is one of the environmental factors which can increase the susceptibility of depression when experiencing chronic stress in the later life. This will further clarify the important roles of early environmental factors in the development of adolescent depression and children rearing conditions should receive more attention.

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1. Introduction

According to World Health Organization (WHO) in October 2015, there were more than 350 million people suffering from depression worldwide [1]. As the leading cause of disability, depression can even lead to suicide.

A wealth of data indicates that chronic stress is an important cause for depression [2–5], which is defined as the nonspecific response of the body to any demand made upon it [6] and must

persist for at least one month [7]. The chronic unpredictable stress paradigm had been established for several decades [8], and later been improved and redefined as chronic unpredictable, variable or intermittent stress and usually sustained for a period of time (ranging from 10 days to 8 weeks) [9,10]. It has been widely used to model depression in rodents [11,12] and was proved to have good predictive validity, face validity and construct validity [13]. In humans, it had also been shown that different adverse life events such as chronic stress due to work, finances or interpersonal conflicts can be main factors that predispose the individuals to depression [14].

However, not everyone who is exposed to chronic stress will develop depressive disorder. In different individuals, it seems as if there is a variation of vulnerability which may be ignored by the investigator. Another neglected factor may be individual differences in the assessment of life stress. To this regard, more and more attention was paid to diathesis–stress theory that individuals with depressive personalities are much more prone to develop depression when exposed to chronic stress [15]. It is estimated that the heritability of depression can be as high as 30%–40% [16], and what is more, clinical researchers have provided tangible evidences to support this theory. They found that when facing stressful life events, individuals with short allele of the serotonin transporter (5-HTT) gene-linked promoter polymorphism exhibited more depressive tendencies than those homozygous for the long allele [17]. Moreover, studies on brain-derived neurotrophic factor (BDNF) gene expression in depressed patients have observed significantly lower mRNA expression as well as lower protein levels compared with controls [18,19]. However, in several other similar studies, results differ considerably. A meta-analysis about the interaction between the 5-HTT gene-linked promoter polymorphism, stressful life events and risk of depression have shown no evidence that the serotonin transporter genotype alone or interact with stressful life events to predict the onset of depression in men alone, women alone, or in both sexes combined [20]. In a study of major depressive disorder (MDD) and bipolar disorder (BPD), no significant differences were found in BDNF gene expression between patients and controls [21]. Given the inconsistent findings mentioned above, it is predicted that there may be another factor besides genetic susceptibility to interact with chronic stress to increase the risk of depression.

A myriad of epidemiological and clinical studies have demonstrated that early adversity is a well-documented risk factor for developing depressive disorders in later life. Many adult depressed patients had a history of exposure to early adversities such as childhood abuse, neglect and loss [16]. Longitudinal studies have also reported significant positive correlation between early adversities and depressive morbidity observed in adults, including maltreatment types, severity, frequency, and duration [22–24]. The more of stressful life events experienced in childhood, the more serious of depressive symptoms developed in later life. In addition, results from twin studies indicate that compared with genetic factors, individuals with early adversities are more likely to develop depressive episodes [25–27]. Unfortunately, most of studies on this issue have focused on the relationship between early adversity and depression in adults and few studies have examined the early-onset depressive disorder. Epidemiological investigations have revealed that the depressive morbidity had the youth oriented tendency and adolescents were proved to be more vulnerable to the damage of glucocorticoids due to increasing glucocorticoid receptor expression in the prefrontal cortex at this age [28]. It is just because the adolescent depression will cause a tremendous burden to society that they should receive more attention.

Nevertheless, many critical factors, such as the onset time, severity and duration of the early adversity and chronic stress cannot be tightly controlled in humans. In order to systematically investigate the impacts of early adversity on adolescents, reliable

animal models should be established. Compared to other experimental animals such as rodents, non-human primates bear a lot of similarities with human, including phylogenesis, brain development, mother–infant bonding, social behaviors, emotion regulation and stress responses [29–31]. All of these similarities make non-human primates as an ideal model to study the influences of early adversity.

Maternal separation can be used to simulate the early adversity experienced by primates, and it is found that six-day maternal separation can induce increased self-mutilation behaviors and decreased social play [32]. Suppressed immune responses and altered brain function have also been observed in non-human primates who experienced maternal separation [33,34]. Moreover, findings in humans have also shown that early parental separation has stronger and wider effects on adult psychopathology than parental death, genetic and environmental influences [35,36].

Our previous studies have also found that early adversity can produce lasting changes in physiology and behaviors in rhesus monkeys [37], but depressive symptoms have not yet been observed. In detail, those maternally separated monkeys showed decreases in locomotion, as well as increases in stereotypical behaviors compared with mother reared monkeys. The deleterious effects of early adversity on rhesus monkeys cannot be compensated by a later normal social life. Nevertheless, the huddling up behavior which is considered to be the core symptom of depression has not been observed. Accordingly, we consider whether the rhesus monkeys experiencing early adversity are more likely to develop depressive symptoms than controls under the conditions of chronic unpredictable stress in their adolescence? Based on this macaque model, our present study investigated the long term relationship between early adversity, chronic stress and adolescent depression for the first time. This will further clarify the important roles of early environmental factors in the development of adolescent depression, and inspire researchers to put more attention to the children rearing conditions and take some effective measures to reverse or improve the negative effects of early adversity.

2. Materials and methods

2.1. Subjects

Eight newborn male rhesus monkeys (*Macaca mulatta*) were selected and randomly divided into two groups: maternal separated (MS, $n=4$) and mother reared (MR, $n=4$). The MS newborns were separated from their mothers at birth and reared solely for the first month in an incubator. Then, the MS infants were paired off and lived together in a steel cage ($0.74 \times 0.71 \times 0.74$ m) for about six months. The MR monkeys had been living with their mothers for seven months since they were born. After that, both the MS and MR monkeys were moved into a connected indoor ($2.61 \times 2.46 \times 2.58$ m)–outdoor ($2.67 \times 2.66 \times 2.67$ m) colony and reared together.

All animal procedures were approved by the National Institute of Health Guide for the Care and Use of Laboratory Animals and were authorized by the Institutional Animal Care and Use Committee of Kunming Institute of Zoology.

2.2. Experimental design

The eight monkeys had been reared together for four years before the chronic stress, and then they were put into an individual cage respectively and reared alone. After one-month adaptation period, several unpredictable chronic stresses were randomly carried out. According to previous studies in rodents [38], four types of stressors were applied in the present study, including space

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