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Research report

Prenatal stress induces vulnerability to stress together with the disruption of central serotonin neurons in mice

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HIGHLIGHTS

- Acute emotional stress response disappeared in naive mice that had been exposed to repeated restraint stress.
- Prenatally stressed mice did not develop this stress adaptation.
- A decrease in tryptophan hydroxylase was observed in stress-maladaptive mice.
- The transcription factor Lmx1b was decreased in the embryonic hindbrain and adult raphe of prenatally stressed mice.

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ABSTRACT

A growing body of evidence suggests that prenatal stress increases the vulnerability to neuropsychiatric disorders. On the other hand, the ability to adapt to stress is an important defensive function of a living body, and disturbance of this stress adaptability may be related, at least in part, to the pathophysiology of stress-related psychiatric disorders. The aim of the present study was to clarify the relationship between exposure to prenatal stress and the ability to adapt to stress in mice. Naive and prenatally stressed mice were exposed to repeated restraint stress for 60 min/day for 7 days. After the final exposure to restraint stress, the emotionality of mice was evaluated in terms of exploratory activity, i.e., total distance moved as well as the number and duration of rearing and head-dipping behaviors, using an automatic hole-board apparatus. A single exposure to restraint stress for 60 min induced a decrease in head-dipping behavior in the hole-board test. This acute emotional stress response disappeared in naive mice that had been exposed to repeated restraint stress for 60 min/day for 7 days, which confirmed the development of stress adaptation. In contrast, prenatally stressed mice did not develop this stress adaptation, and still showed a decrease in head-dipping behavior after the repeated exposure to restraint stress. Biochemical studies showed that the rate-limiting enzyme in 5-HT synthesis, tryptophan hydroxylase, was increased in raphe obtained from stress-adapted mice. In contrast, a decrease in tryptophan hydroxylase was observed in stress-maladaptive mice. In addition, the transcription factor Lmx1b, which is essential for differentiation and the maintenance of normal functions in central 5-HT neurons, was decreased in the embryonic hindbrain and adult raphe of prenatally stressed mice. These findings suggest that exposure to excessive prenatal stress may induce a vulnerability to stress and disrupt the development of 5-HT neurons.

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1. Introduction

Depression and anxiety disorders are common public health problems with a lifetime prevalence of 10–20%, yet the mechanisms that underlie their pathophysiology are still poorly understood. Most pregnant women are at risk of showing some emotional abnormality, since some biological functions such as hormonal systems may dramatically change during pregnancy. Indeed, it has been reported that 16% of women experience the onset of an affective disorder during pregnancy, and 68% of them showed symptoms during the first trimester [1]. Thus, a suitable management plan that includes drug therapy may be necessary for pregnant women. However, doctors hesitate to use positive drug therapies because of worries regarding adverse effects on the embryo. Inappropriate mental support for pregnant women may result in their exposure to very stressful situations. Particularly when pregnant women suffer from serious mental disease, inappropriate drug therapies could expose them to very severe stressful situations. Previous clinical

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research on pregnant women suffering depressive disorders indicated that the activity of the fetus and newborn is elevated, prenatal growth is delayed, and prematurity and low birthweight are more frequent [2]. Moreover, it has also been suggested that exposure to stress during gestation may impair the emotional development of the offspring and, as a result, the incidence of several neuropsychiatric disorders, including depression, anxiety, schizophrenia, and autism, may increase [3–5]. Additionally, preclinical studies have suggested that offspring exposed to prenatal stress show abnormal psychiatric behaviors such as increased fear and anxiety [6,7], persistent paradoxical sleep alterations [8], deficits of learning and memory [9,10], depressive-like behavior [11–13] and schizophrenia-like behavior [14]. Moreover, prenatal stress induces several functional and structural abnormalities of the components that regulate stress responses, such as the hypothalamic-pituitary-adrenal (HPA)-axis [15,16] and monoamine neurotransmission [17–19]. However, the mechanisms that underlie the impact of prenatal stress on adulthood are not yet fully understood.

Axons from the neurons of the raphe nuclei, the principal source of serotonin (5-hydroxytryptamine; 5-HT) released in the brain, form a neurotransmitter system that reaches almost every part of the central nervous system. Based on clinical and preclinical studies, it has been widely accepted that central 5-HT neurotransmission may be involved in the etiology, expression and treatment of anxiety, impulsiveness and depression [20,21]. A few preclinical reports have suggested that prenatal stress could affect central 5-HT neurons. Peters et al. reported that maternal stress increased fetal brain 5-HT synthesis in rat. They also found that offspring that had been exposed to prenatal stress showed region-specific changes in brain 5-HT, 5-hydroxyindoleacetic acid (5-HIAA) and noradrenaline levels in infancy [17]. Hayashi et al. reported that maternal stress induced synaptic loss associated with the disruption of 5-HT neurotransmission and developmental disabilities in offspring [9]. In addition to these precedent articles, we recently reported that offspring that had been exposed to strong prenatal stress displayed an increase in anxiety-like behavior as determined by the elevated plus-maze test together with disruption of the development of 5-HT neurons in mice [22].

On the other hand, the ability to adapt to stress is an important defensive function of a living body, and impairment of this ability may contribute to some stress-related disorders. Thus, the identification of brain mechanisms that contribute to stress adaptation could help pave the way for new therapeutic strategies for stress-related psychiatric disorders. A series of behavioral experiments have demonstrated that repeated exposure to the same type of stress stimuli diminishes acute stress responses. For example, Kennett and co-workers reported that male rats that had been exposed to a single restraint stress for 120 min exhibited a reduction in locomotor activity in an open field, but this change in behavior disappeared after repeated exposure to restraint stress for 120 min/day for 7 days [23–25]. Similar behavioral adaptive responses to stress stimuli in rats have been confirmed by other researchers [26–28], which suggest that this animal model may be useful for investigating the mechanisms of stress adaptation. Furthermore, we examined behavioral responses in rats that were produced by either single or repeated exposure to restraint stress for 60 or 120 min. A single exposure to restraint stress reduced locomotor activity, and this stress response disappeared in rats that were exposed to repeated restraint stress for 60 min/day for 7 days, which confirmed the development of stress adaptation. However, this adaptive response to stress stimuli was not observed in rats that had been exposed to restraint stress for 240 min/day for 7 days. Thus, we can create stress-adaptive and -maladaptive models by repeatedly exposing rats to different degrees of restraint stress [29]. In addition, more recently, to further characterize models of stress adaptation, we created stress-adaptive and -maladaptive models in mice, as described below [30]. A single exposure to restraint stress for 60 min produced a decrease in the number and duration of head-dipping behaviors of mice in the hole-board test, and these acute emotional responses were recovered by exposure to repeated restraint stress for 60 min/day for 7 or 14 days, but not 3 days. However, mice that had been exposed to repeated restraint stress for 240 min/day for 7 or 14 days continued to show a decrease in head-dipping behavior in the hole-board test. Furthermore, the results obtained in our previous studies suggest that the brain 5-HT nervous system may be involved, at least in part, in the development of adaptation to stress [31–33].

The aim of the present study was to clarify the influence of exposure to prenatal stress on the development of stress adaptation and central 5-HT neurons.

2. Materials and methods

The present studies were conducted in accordance with the Guide for the Care and Use of Laboratory Animals as adopted by the Committee on the Care and Use of Laboratory Animals of the International University Health and Welfare.

2.1. Animals

All experiments were performed using 8-week-old male offspring of ICR mice (Japan SLC, Inc., Shizuoka, Japan) that had been prenatally exposed to stress as described below, or naive mice. The mice were housed at a room temperature of $23 \pm 1\,^{\circ}C$ and humidity of $50 \pm 5\%$ with a 12 h light-dark cycle (light on 7:00 a.m. to 7:00 p.m.). Food and water were available ad libitum.

2.2. Experimental procedure

2.2.1. Exposure to prenatal stress

Virgin female mice were mated at 10–11 weeks of age. The presence of a copulation plug denoted gestation day (GD) 0.5. Pregnant females were housed individually. In the model mice exposed to prenatal restraint stress (PRS), the pregnant mice were placed in a 50 (for mice with a body weight of 40 g or less)- or 70 (for mice with a body weight of 40 g or more)-ml polystyrene tube at 6 h (10:00 a.m. to 4:00 p.m.) a day from GD 5.5 to GD 17.5. The conditions of exposure to restraint stress to pregnant mice were determined in accordance with our previous study [22].

2.2.2. Effects of exposure to acute restraint stress on the emotionality of mice as estimated by the hole-board test

8 week-old naive or prenatally stressed mice were exposed to single restraint stress for 60 min by being inserted into a syringe (50 mL) or left in their home cage in adulthood. Just after the exposure to restraint stress, the emotionality of mice was estimated by the hole-board test [34,31]. Namely, each mouse was placed in the center of the hole-board and allowed to freely explore the apparatus for 5 min. The exploratory behaviors of mice on the hole-board, i.e., distance moved, the number and duration of rearing, and the number and duration of head-dips, were automatically recorded.

2.2.3. Effects of exposure to repeated restraint stress on the emotionality of mice as estimated by the hole-board test

8 week-old naive or prenatally stressed mice were exposed to restraint stress for 60 min/day for 7 days. Just after the exposure to final restraint stress, the emotionality of mice was estimated by the hole-board test. At the end of the experiments, the brain samples for western blotting or immunohistochemistry were collected.

2.3. Apparatus for the hole-board test

To investigate the changes in general emotional behaviors, mice were tested using an automatic hole-board apparatus (model

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