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Cognitive and affective alterations by prenatal and postnatal stress interaction

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HIGHLIGHTS

- Some functional alterations by prenatal stress are independent of stressor types.
- Other functional alterations by prenatal stress are distinct between stressor types.
- Prenatal stress-induced alterations may be adaptive against postnatal stress.

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ABSTRACT

Antenatal maternal stress exposure during pregnancy has been shown to alter the neurodevelopment of fetuses, and consequently affect brain function in offspring after birth. In this study, we investigated the effects of prenatal exposure to social and nonsocial stress on cognitive and affective functions in mice. Pregnant mice were subjected to repeated social defeat stress or restraint stress, and the offspring born from the dams were subjected to a battery of behavioral tests to assess cognitive and affective functions. Heightened anxiety and decreased social interaction with mates were observed in adult mice exposed to prenatal social defeat and restraint stress. In contrast, spatial memory was impaired by prenatal restraint stress, but not social defeat stress. In addition, prenatal stress-induced heighted anxiety and decreased social interactions were still present, whereas spatial memory impairment was not observed, when postnatal chronic stress exposure during the juvenile period was matched with the prenatal stress type (i.e., restraint stress). These results suggest that some neurodevelopmental changes associated with prenatal stress may counteract with postnatal stress-induced alterations. Therefore, prenatal stress-induced neurodevelopmental changes may be understood to be adaptive strategies against anticipated postnatal adverse environments.

1. Introduction

Severe, chronic stress yields adverse effects on brain function and neurodevelopment, depending on the timing of exposure [1]. Such stress has been suggested to play significant roles in psychiatric disorders, such as schizophrenia and major depressive disorder, attributed to onset, precipitation, and exacerbation of symptoms [2–4].

Antenatal maternal stress during pregnancy alters neurodevelopment and consequently, the brain function of offspring. Epidemiological studies have shown that offspring born from mothers who experienced stress during pregnancy exhibit increased risks of psychiatric disorders and a deterioration of cognitive function [5–10]. Animal model studies, mostly conducted in rodents, have confirmed these findings, along with unveiling the biological mechanisms underlying the effects of prenatal stress [11]. Studies have shown that rodents exposed to prenatal stress exhibit behavioral alterations such as spatial memory deficits [12–14], decreased social interaction with mates [15,16], and heightened anxiety [16,17]. Consistent with these behavioral alterations, prenatal stress also alters morphological and functional synaptic connectivity in the corticolimbic neural network, which consists of the hippocampus, the prefrontal cortex (PFC), and the amygdala [15,16,18–22].

Stress is associated with various environmental factors, but these factors can be roughly divided into social vs. nonsocial (physical) stress. Nonsocial stress frequently used in rodent studies, including prenatal stress exposure, include such as restraint [13] and elevated platform [23] stress, whereas social stress procedures include stress induced by social defeats [24], social mixing [25], and social crowdedness [26]. Nevertheless, there have been few studies that have directly evaluated whether prenatal exposure to social and nonsocial stress yield similar, if not identical, effects. In this regard, it is of particular interest to note that restraint and unpredictable stress, two different types of stressors have been demonstrated to cause the contrasting neuronal and

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behavioral changes in adult animals [27,28], suggesting that the type of stressor may play an important role in determining stress-induced neuronal alterations. It remains unclear whether prenatal stress-induced changes also depend on stressor type.

Another issue that has remained mostly elusive is whether and how prenatal stress-induced neurodevelopmental changes interact with postnatal re-exposure to stress. Indeed, stress occurrences are life-long events that happen multiple times throughout life. Several studies have demonstrated that prenatal stress-induced changes, such as spatial memory impairment and heightened anxiety, are attenuated by postnatal environments, such as environmental enrichments and handling of animals [17,29]. Emerging evidence has suggested that prenatal stress-induced changes also interact with postnatal stress. For instance, Dunlap and colleagues have shown that either prenatal or postnatal stress alone impairs copulatory behaviors in male animals. In contrast, animals exposed to both prenatal and postnatal stress do not exhibit such impairments [30], suggesting the possibility that prenatal stress-induced neurodevelopmental changes may have some adaptive values for coping with postnatal stress.

In this study, we investigated the effects of social and nonsocial prenatal stress on cognitive and affective function in mice using a battery of behavioral tests. To further understand the impacts of social and nonsocial prenatal stress, we also examined how alterations caused by prenatal stress interacted with postnatal stress by re-exposing mice to postnatal social and nonsocial stress. Therefore, our hypotheses were two fold. First, prenatal social and nonsocial stress might induce distinct patterns of cognitive and affective alterations in offspring. Second, prenatal stress-induced alterations might counteract postnatal stress by which prenatal stress-induced alterations were normalized. Alternately, for the later hypothesis, it is also possible that prenatal stress-induced alterations are augmented by postnatal stress, depending on the conditions, such as when prenatal and postnatal stress types are incongruent, as recently suggested by Bock et al. [31].

2. Materials and methods

2.1. Animals

All experiments were conducted in accordance with the *Science Council of Japan Guidelines for Proper Conduct of Animal Experiments* and approved by the Kyoto University Primate Research Institute Animal Experiment Committee. Adult male and female CD1 mice were purchased from Charles-River Japan, and a pair of male and female mice were housed in each cage. The first day of plug confirmation was determined as gestational day (GD) 1, and male mice were removed from the cage thereafter. Male and female offspring born from mothers were reared together until postnatal day (PD) 21, at which they were weaned into 2–3 mice of the same sex per cage. To exclude a potential kin bias, no >3 offspring from each dam were used. In total, 15 dams and fetuses were used for stress hormone assays, and 150 offspring born from 59 dams were used for behavioral tests.

2.2. Prenatal and postnatal stress

Restraint and social defeat stress procedures were employed for nonsocial and social stress, respectively. Pregnant mice were exposed to prenatal restraint and social defeat stress for 5 days starting at GD14 (Fig. 1). For prenatal restraint stress, a dam was placed in a 3-cm diameter nontransparent plastic cylinder for 1 h per day. For prenatal social defeat stress, a dam was introduced into a cage where another female was residing for 1 h per day. The cage was divided by a mesh wall when introducing a dam into a cage, such that direct fighting between the dam and the resident female was prevented during confrontation. The resident female was housed together with a male partner, which was removed during the confrontation. For some animals, their offspring were exposed to postnatal restraint or social defeat stress for 14 days from PD28 to PD42 (Fig. 1). These mice were placed in a cylinder for 1 h per day for restraint stress or introduced into a cage where a male or female mouse (depending on the gender of intruder, such that intruder/resident pairs were of the same sex) was residing for social defeat stress. A control group of mice were food/water-deprived for 1 h per day over 5 days in their home cages. Control animals were subjected to this treatment, because stressed mice were also under 1 h of food/water deprivation during each day of stress exposure. Depending on the stress treatment, there were 7 experimental groups, as follows; (1) prenatal social defeat stress (SS); (2) prenatal restraint stress (RS); (3) prenatal social defeat and postnatal social defeat stress (SS-SS); (4) prenatal social defeat and postnatal restraint stress (SS-RS); (5) prenatal restraint and postnatal restraint stress (RS-RS); (6) prenatal restraint and postnatal social defeat stress (RS-SS); and (7) no stress (control, or CTR).

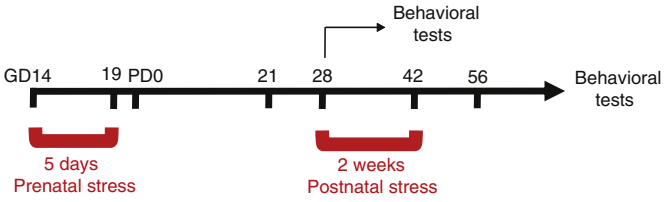

Fig. 1. A schematic diagram illustrating the experimental timeline. Prenatal stress was given for 5 days starting at GD14, which corresponds to the late gestational period. In some animals, postnatal stress was also given for 14 days from PD28 to PD42, which corresponds to the late juvenile and the early adolescent period. Behavioral tests were conducted at either PD25-35 or PD56-63, which correspond to the juvenile period and young adulthood, respectively.

2.3. Behavioral tests

A battery of behavioral tests was conducted to examine the effects of prenatal and postnatal stress interactions in the offspring at PD28-35 or PD56-63, which corresponds to the juvenile period or young adulthood, respectively (Fig. 1). These behavioral tests were conducted consecutively in a fixed order (in the order of the subsections below), and were completed in <1 week. These tests were selected to examine functions of the corticolimbic system.

2.3.1. Locomotion

Spontaneous locomotion in a novel environment was examined to evaluate motor control and response to novelty. Animals were placed in an open field chamber (40 × 40 × 40 cm). The horizontal distance travelled in 20 min and the percentage of time that the mice were present in a 20 × 20 cm central area of the chamber were measured. Animals with less anxiety have been shown to approach the central area of the open field chamber more often [32].

2.3.2. Elevated plus maze

The elevated plus maze test was conducted to examine anxiety of the animals, which has been associated with affective corticolimbic circuitry, with the amygdala in its center [33,34]. The maze consisted of 2 opened arms (50 × 5 cm) facing each other and 2 closed arms by the walls (20 cm high) that were located perpendicular to the opened arms. These arms were elevated 1 m from the ground. A mouse was placed in the central arena and allowed to freely explore the arms for 10 min. The total time spent in the opened and closed arms was measured. The amounts of time that the animals spent in the opened and closed arms indicate the anxiety state of the animals, where more or less time spent in the opened arm reflect lower and higher anxiety levels, respectively.

2.3.3. Three chamber social test

Social interactions with mates has been shown to be rewarding and associated with dopamine (DA) transmission in the corticolimbic