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Behavioral deficits, abnormal corticosterone, and reduced prefrontal metabolites of adolescent rats subject to early life stress

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HIGHLIGHTS

- Early life stress induced depressive-like behavior in adolescent rats.
- Early life stress increased corticosterone level in adolescent rats.
- Early life stress reduced prefrontal glutamate, glutamine, and N-acetylaspartate.
- The findings underscore the long-lasting and detrimental effects of childhood adversities.

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ABSTRACT

The present study investigated the effect of early life stress in adolescent rats on brain metabolites, serum corticosterone, and depressive-like behavior. A group of rats was subject to early life stress from postnatal day (PND) 1 to 14. A matched control group was studied. Behavioral tests, serum corticosterone and high-resolution proton magnetic resonance spectroscopy were conducted between PND 30 and 40. In this study, adolescent rats exposed to early life stress demonstrated depressive-like behavior and increased serum corticosterone during adolescence. They also showed reduced glutamate, glutamine, and N-acetylaspartate (NAA) levels in the prefrontal cortex. A reduced myo-inositol level, consistent with astroglial deficits, was observed but was not statistically significant. Together, these findings characterize the effect of early life stress on adolescent animals and underscore the long-lasting and detrimental effects of childhood adversities.

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1. Introduction

Major depressive disorder is a debilitating mental illness and worldwide leading cause of disability [31]. Environmental risk factors, especially early life stress, appear to play a pivotal role in the pathophysiology of major depression [12]. Therefore, investigating the neurobiological mechanisms of early life stress is essential for a better understanding of major depression, and perhaps other stress-related psychiatric disorders [12]. Clinical studies have associated history of child abuse with abnormal neuroendocrine responses and increased risk of major depression [11]. Moreover, the prefrontal cortex and the hippocampus, two brain regions implicated in stress response, were found to have reduced volume in adults exposed to early life stress [3,35]. Consistent with these human findings, preclinical evidence from both rodents and nonhuman primates showed behavioral deficits with long-term neurobiological alterations induced by early life stress [7,22]. Thus, early life stress in animals provides a unique model for investigating the neurodevelopmental mechanisms of major depression.

Adolescence is a vital phase of development demonstrating high neuroplasticity and sensitivity to early adverse events [21]. Several neuropsychiatric disorders, including major depression, may first present during adolescence [1,25]. Yet, the effects of early adversities have not been extensively studied in adolescent animals. A

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study by Ichise et al. reported abnormalities in the serotoninergic system of peer-reared non-human primates adolescents [15]. However, the developmental effects of early stress on the glutamatergic system are not well understood.

The aim of the current study was to examine whether early life stress will induce depressive-like behavior and alter the glutamatergic system in adolescent rats. For this purpose, we used proton magnetic resonance spectroscopy (^{1}H MRS) to quantify the level of glutamate and other brain metabolites in the prefrontal cortex. The prefrontal cortex was selected as the brain region of interest given its crucial role in emotional regulation and stress response [17]. Metabolites measured by ^{1}H MRS included: glutamate, glutamine, N-acetylaspartate (NAA), choline compounds (Cho), myo-inositol, and creatine (Cr). For detailed description of the physiologic function of these metabolites please see the recent review by Maddock and Buonocore [20]. Briefly, glutamate and glutamine are an amino acid neurotransmitter and its derivative, respectively. Their levels may reflect local neuronal activity. NAA, the most abundant neuronal amino acid, is commonly used as a marker of neuronal integrity. Cho increases have been interpreted to reflect increased cell membrane turnover, and myo-inositol was associated with astroglial metabolism. Cr increases have been associated with increased myelination, however, Cr tends to be stable in the absence of major pathology [20]. Prior ^{1}H MRS studies in neonatal [19] and adult [13,14] animals exposed to early life stress have reported altered levels of glutamate, NAA, Cho, and myo-inositol. The current study extends prior evidence to investigate the developmental effect of early life stress on prefrontal metabolites in adolescent rats.

2. Materials and methods

2.1. Animals

Parental Sprague-Dawley rats were purchased from Animal Center of Shantou University Medical College and mated (one male with two females) in Shantou University Mental Health Center animal facility two weeks after their arrival. A total of 32 rats were studied. The early life stress group had 8 males and 8 females. Similarly, the control group had 8 males and 8 females. All animals were housed in a temperature ($22 \pm 1\,^\circ$C) and humidity ($55 \pm 4\%$) controlled room on a 12-h light/dark cycle (lights on at 07:00 a.m.) with food and water provided *ad libitum*. All experimental procedures were in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and approved by Laboratory Animals Care and Use committee of Shantou University Medical College.

2.2. Early life stress

The early life stress protocol was conducted as previously described [5]. Briefly, dams were first removed and pups were separately placed in a plastic container with bedding from the fostering cage. Pups were moved to an adjacent room keeping constant temperature with 34 °C during separation period. The separation procedure was conducted for 180 min (08:30 a.m. and 11:30 a.m.) from PND 1 to 14. After separation, the pups and dams were reunited at the maternity cages. Animals in the control group were left with their mothers undisturbed between PND 1 and 14, with the exception of the weekly cage cleaning.

2.3. Behavioral tests

All behavioral tests took place during adolescence between PND 30 and 38 [18]. The sequence of behavioral tests was based on our previous report [16]. Sucrose preference and forced swimming tests were selected given their relevance to depression symptoms of anhedonia and despair, respectively [24].

2.3.1. Sucrose preference test

Sucrose preference test was conducted as previously described [16], with minor modification. In summary, single-housed animals were habituated to 1% sucrose solution for two days followed by 24 h food and water deprivation. Then, animals were exposed for 3 h to two identical bottles, one filled with water and the other with 1% sucrose. The position of bottles was counterbalanced across the left and right side of the test cages. Sucrose preference was calculated as follow: sucrose consumption percentage = sucrose consumption/(sucrose consumption + water consumption) × 100.

2.3.2. Forced swimming test

Forced swimming test was performed according to previous reports [23,28]. Rats were placed individually in a transparent cylindrical tank (30 cm in diameter, 50 cm height) containing water at 23–24 °C with a 30 cm depth. All animals were exposed to 15 min swimming, 24 h prior to the 5 min swimming test. Immobility time (rats floated without struggling or making least movements necessary to keep their heads above the water) was scored from videotapes by two trained observers who were blind to the experimental conditions. The agreement between the two observers was substantial with a kappa coefficient = 0.65.

2.4. Serum level of corticosterone

Trunk blood samples were collected at PND 40 between 10 a.m. and 12 p.m. Serum was taken after blood samples centrifuged at $1200 \times g$ for 30 min, then frozen at −80 °C. Serum corticosterone levels were measured using Corticosterone ELISA kit (Abcam LLC, Cambridge, UK). The range of detectable level is 20–400 ng/ml.

2.5. ^{1}H MRS acquisition and processing

At PND 40, animals were rapidly decapitated without anesthesia. The whole brain was rapidly removed from the skull and put on dry ice immediately. Olfactory bulbs were firstly removed followed by cutting out bilateral prefrontal cortex according to a rat brain atlas [26], which included the anterior cingulate, infralimbic, prelimbic, and ventrolateral orbitofrontal cortices. The dissected region coordinates were as follow: Anterior – 4.2 mm anterior to bregma, 2.4 mm lateral to midline, 2.2 mm ventral to the skull; Posterior – 2.2 mm anterior to bregma, 2.4 mm lateral to midline, 5.5 mm ventral to the skull. Additional detail on prefrontal cortex of rat can be found in Ref. [34]. The bilateral prefrontal cortices – and other brain regions (not reported here) – were stored at −80 °C until analysis. The preparation of the brain samples was based on our previous report [4]. Frozen brain tissue was homogenized with pestle mixed with 0.5 M ice-cold perchloric acid for 15 min on dry ice. The homogenate was centrifuged at $10{,}000 \times g$ for 20 min at 4 °C. The supernatant was neutralized with 1.0 M KOH and lyophilized for about 36 h. Dried extracts were suspended in 500 μl D_2O containing 2,2′-3,3′-tetradeutero-trimethyl-sylilpropionate (TMSP), and then transferred into 5 mm nuclear magnetic resonance tubes for ^{1}H MRS detection.

All ^{1}H MRS data were acquired on BrukerAvance 400 MHz high-resolution (9.4 T) magnetic resonance spectrometer (Bruker Co., Germany). Free induction decays (FIDs) were collected on 4096 data points over a spectral width of 5000 Hz with a relaxation delay of 5 s and the number of scans was 128. Spectra processing included Fourier-transformation, phase correction and baseline correction, using XWINNMR (Bruker GmBH). The calculation of metabolites concentration was based on previous reports [4,10]. The chemical shifts were assigned according to the external

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