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Repeated fluvoxamine treatment recovers early postnatal stress-induced hypersociability-like behavior in adult rats

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ABSTRACT

Childhood maltreatment is associated with impaired adult brain function, particularly in the hippocampus, and is not only a major risk factor for some psychiatric diseases but also affects early social development and social adaptation in later life. The aims of this study were to determine whether early postnatal stress affects social behavior and whether repeated fluvoxamine treatment reverses these changes. Rat pups were exposed to footshock stress during postnatal days 21–25 (at 3 weeks old: 3wFS). During the post-adolescent period (10–14 weeks postnatal), the social interaction test and Golgi-cox staining of dorsal hippocampal pyramidal neurons were performed. Following exposure to footshock stress, 3wFS rats showed an increase in social interaction time, which might be practically synonymous with hypersociability, and a decrease in spine density in the CA3 hippocampal subregion, but not in CA1. These behavioral and morphological changes were both recovered by repeated oral administration of fluvoxamine at a dose of 10 mg/kg/day for 14 days. These findings suggest that the vulnerability of the hippocampal CA3 region is closely related to social impairments induced by physical stress during the juvenile period and shed some light on therapeutic alternatives for early postnatal stress-induced emotional dysfunction.

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Introduction

Childhood maltreatment is a serious social issue and has a severe impact on both physical development and mental health in adulthood. In fact, early postnatal stress enhances susceptibility to physical and/or emotional stress and can be one of the factors contributing to psychopathology, such as posttraumatic stress disorder (PTSD), attention-deficit/hyperactivity disorder, and other behavioral problems.[1] PTSD was categorized as an “Anxiety Disorder” in the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)[2] but was subsequently moved to the “Trauma- and Stressor-Related Disorders” category in DSM-5.[3] Disinhibited Social Engagement Disorder (DSED) is also included in this category.[3] Children with DSED are hypersociable, seeking comfort and affection nonselectively, even from unknown adults, and they have difficulties in forming close, confiding relationships.[4] These clinical entities can develop into emotional dysregulation, such as depression, dissociative disorders, and borderline personality disorders,[5] and often cause many problems, such as an abnormal personality or antisocial behavior.[6]

In clinical studies, adults with PTSD related to childhood maltreatment have been shown to have a small frontal cortex, corpus callosum, and hippocampus relative to healthy control subjects, as measured via magnetic resonance imaging.[7,8] Hippocampal size is susceptible to childhood maltreatment, especially that occurring between the ages of 3 and 5; exposure of the immature hippocampus to corticotropin-releasing hormone results in an adverse effect on cell survival and dendritic branching.[8] The use of chronic restraint stress for 21 days, a rodent stress model, causes increased corticosterone (CORT) levels, resulting in shortened dendritic length and reduced branch number in hippocampal CA3 apical dendrites.[9,10] Thus, stress-induced hypothalamic-

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pituitary-adrenal (HPA) axis hyperactivity is considered to significantly affect the formation of the neuronal network as a consequence of changes in dendritic morphology, as well as neuronal cell death.

As we have previously reported, exposure to footshock (FS) stress from postnatal days 21–25 (at 3 weeks old: 3wFS) causes behavioral abnormalities in adulthood.[11–13] For example, 3wFS rats showed an increased ratio of time spent in the open arms during the elevated plus-maze (EPM) test and of immobility time during the forced swim test (FST). Extinction of contextual fear conditioning was also significantly impaired in the 3wFS group compared with the control group. Furthermore, Lyttle et al. reported that 3wFS rats exhibited reduced spine densities and dendritic lengths of layer II/III pyramidal neurons in the infralimbic cortex, and that repeated treatment using fluvoxamine, a selective serotonin reuptake inhibitor (SSRIs), recovered the increased immobility during the FST and the reduced spine densities/dendritic lengths observed in the 3wFS group.[13] While early postnatal stress may induce behavioral and morphological changes, the impact of these early negative experiences, especially punishment, on subsequent social behavior remains poorly studied.

Thus, the purposes of the present study were to examine the effects of early postnatal exposure to FS stress on social interaction time and dendritic spine density in the hippocampus in adult rats, and to assess whether the repeated administration of fluvoxamine affects these behavioral and morphological changes.

Materials and methods

Animals

Male Wistar/ST rats were used. All rats were the offspring of timed pregnant rats supplied by Nippon SLC Co. Ltd. (Hamamatsu, Japan) The day of birth was denoted as postnatal day 0 (PND 0). Gender was determined on PND 14, and weaning occurred on PND 21. The rats were housed in a room with a 12 h light–dark cycle (light on at 19:00) and a temperature-controlled environment (21 ± 2 °C) with food and water *ad libitum*. All animals were treated in accordance with the guidelines for the Care and Use of Laboratory Animals of the Animal Research Committee of Hokkaido University.

Early postnatal stress

The rats were subjected to early postnatal stress as previously described.[11–13] Briefly, daily footshock stress was applied during PND 21–25 (3wFS) by placing each animal in an individual chamber with an electrified grid floor that delivered five unavoidable shocks (intershock interval, 30 s; shock duration, 2 s; shock intensity, 0.5 mA), using a programmable shock generator and scrambler (Med Associates Inc., St. Albans, VT, USA). Rats in the control group were placed in home cages without footshock on postnatal days 21–25 (NONFS).

Two experiments were conducted using these rats (Fig. 1): behavioral changes in the post-adolescent period (10–14 weeks old) were assessed as described below (Experiment 1) and pharmacological effects of fluvoxamine on both behavioral and morphological changes in the hippocampus of adults were investigated (Experiment 2). Rats were adapted to handling for 3 days before behavioral tests were performed.

Social interaction (SI) test

The apparatus used for the SI test was a solid plastic box (60 cm × 60 cm × 40 cm) with an open roof. Rats were placed singly in the experimental box for 10 min for 3 consecutive days prior to the SI test. This habituation session allowed the rats to become familiar with the experimental box environment. To evaluate locomotor activity, the distance traveled, the total number of zone crossings (number of times animals crossed the lines dividing the open field into 6 × 6), and the time spent in the center area were recorded, and were automatically analyzed using the LimeLight2 software package (Actimetrics Inc., Wilmette, IL, USA). On day 4, each rat was tested for SI with an unknown test partner. The general design of the SI test was adapted from a previous report.[14] Pairs of weight-matched (±20 g) rats, unfamiliar with each other, were simultaneously placed in the SI box for an observation period of 10 min. Behavior was recorded on a PC hard drive, and locomotor activity for pairs of rats was calculated using LimeLight2. Active contacts (i.e., sniffing, following, mounting, and genital investigation) and SI time were measured using visual observation. All tests were carried out under a low-light condition (20 lux light located above the experimental box), during the dark phase of the day, between 08:00 and 16:00 (Fig. 1; (A) Experiment 1).

Drug treatment

Fluvoxamine maleate (10 mg/kg/day, Wako, Japan) or vehicle (purified water) was administered orally at a volume of 5 ml/kg from PND 26, once per day for 14 days. The dose of this drug was based on a previous study.[13] In the post-adolescent period (10–14 weeks old), behavioral experiments were performed (Fig. 1; (B) Experiment 2).

Golgi-cox staining procedure

After completion of all behavioral tests, animals were anesthetized with sodium pentobarbital (60 mg/kg, i.p.) and then rapidly decapitated. The brains were removed and processed for Golgi staining according to the manufacturer's protocol (FD Rapid GolgiStainTM Kit; FD Neurotechnologies, Inc, USA). In brief, freshly dissected brains were kept in impregnation solutions (A and B) for 3 weeks in the dark, at room temperature. After being transferred into solution C for 48 h at 4 °C, brain tissues were sectioned into 120 μm slices using a cryostat (Thermo Scientific HM 500 microtome, kept at −22 to −25 °C) and fixed to gelatin-coated slides in a drop of Golgi solution C. Excess Golgi solution C was removed from the slide with filter paper, and slides were allowed to dry in the dark at room temperature for 1–2 weeks. A mixture of solutions D, E, and distilled water (1:1:2 ratio) were used for 10 min to stain pyramidal neurons, followed by dehydration in 50%, 75%, 95%, and 100% ethanol (4 min each rinse). The brain sections were cleared in xylene for 8 min and coverslipped with Entellans®. Slides were stored at room temperature in a dark location.

Dendritic spine analysis

Dendritic spine analysis was performed as previously described.[13] Briefly, pyramidal neurons from the CA3 and CA1 regions of the dorsal hippocampus were selected for analysis. Two to three neurons each from 2 to 4 rats in each group (total of 12 rats) were chosen randomly for dendritic spine analysis based on the following criteria: 1) fully impregnated, 2) relatively isolated from nearby neurons, 3) triangularly shaped soma, and 4) clearly visible spines. Photomicrographs were acquired using an Olympus BX50 light microscope with a 40 × objective. Individual spines were distinguished using contrast adjustment and were quantified in the ImageJ/Fiji program (Rasband, WS, ImageJ, US National Institutes of Health, Bethesda, MD, USA) according to the method described by Orlowski and Bjarkam.[15] Apical spine density was assessed by the

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