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Effects of maternal separation, early handling, and standard facility rearing on orienting and impulsive behavior of adolescent rats

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Abstract

Effects of maternal separation in rats have been extensively investigated, but no studies have examined its effects in rat adolescence. We examined the effects of neonatal infant-mother separation (MS) for 6 h/day and early handling (EH) for 10 days during the first 2 weeks of life by comparing MS and EH groups to standard facility reared (SFR) controls. At adolescence, the animals were evaluated in a novel and familiar open-field, the light–dark box, and the sucrose consumption test. Behavioral indices included orienting behavior (rearing frequency and duration), impulsive behavior (movement velocity and risk taking by entering the center of the open field or the light compartment of the light–dark box), hyperactivity (ambulatory distance and stereotypic movement), and reward-seeking behavior (sucrose drinking time). The prolonged MS during the first 2 weeks of life resulted in decreased orienting behavior and increased impulsive behavior in adolescence. Measures of ambulatory and stereotypic movements showed that MS rats were hyperactive in the novel environment whereas EH rats were less active overall. The impulsive/hyperactive phenotype produced by this MS protocol may provide a useful animal model to investigate the neurological basis for the similar behavioral phenotype found in attention deficit/hyperactivity disorder.
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1. Introduction

Early childhood stress has been linked to psychopathology later in life (Anisman et al., 1998; Teicher et al., 2003). Animal studies are an efficient way to explore the long-term effects of early stress. This study used the maternal separation paradigm as a source of early stress. Separating infant rats from their mothers during their first 2 weeks of life is a very stressful event, primarily because pups are totally dependent on their mothers at this age (Janus, 1987).

Maternally separated (MS) animals have been intensively studied for decades and have also served as models of psychopathology (Ellenbroek and Riva, 2003). However, different behavioral phenotypes have been reported depending on different MS protocols, with some studies reporting hyperactive behavior (Arnold and Siviy, 2002; Braun et al., 2003; Kaneko et al., 1994; von Hoersten et al., 1993), others reporting decreased activity (Janus, 1987; Matthews and Robbins, 2003), and still others reporting no difference in activity (Rhees et al., 2001; Shalev and Kafkafi, 2002; Stanton et al., 1992).

Different results have also been reported regarding fearful/anxiety-like behavior after different MS protocols, with most schedules of separation leading to increased fearful/anxiety-like behavior (Barna et al., 2003; Hofer, 1976; Janus, 1987; Kalinichev et al., 2002; Penke et al., 2001). However, other investigators have reported decreased fearfulness and decreased orienting/attentive behavior in adult rats after 6 h/day of MS for 10 days during the first 2 weeks of life (Kaneko et al., 1994), which is a behavioral phenotype similar to that found in attention deficit hyperactivity disorder (ADHD) (Gonzalez-Lima, 2005) and results in brain changes linked to psychopathology (Jimenez-Vasquez et al., 2001). Therefore, we used the same MS protocol to investigate whether adolescent rats would show an impulsive/hyperactive behavioral profile, similar to that found in ADHD.

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Specifically, we examined the effects of neonatal MS and early handling (EH) on measures of orienting, impulsive, and reward-seeking behavior in adolescent rats. These behaviors were tested using the open-field test, the light–dark test, and the sucrose consumption test. We decided to focus on adolescent, as opposed to adult rats, because of the limited knowledge about the effects of maternal separation in rat adolescence. Moreover, from a clinical standpoint, it would be useful to identify individuals at risk for psychopathology during childhood and adolescence prior to adult onset of disease, and behavioral markers present during this period of development in the MS rat may inform this question.

2. Materials and methods

This study was conducted in accordance with the guidelines of the National Institutes of Health and the American Association for the Accreditation of Laboratory Animal Care and was approved by the Institutional Animal Care and Use Committee.

2.1. Subjects

Mothers were pregnant Sprague–Dawley female rats obtained from a commercial supplier (Harlan, Houston, TX) at 14 days of gestation. Pregnant females were singly housed and maintained on a 12-h light–dark cycle in a temperature (22 °C) controlled room inside clear plastic cages (45 cm × 24 cm × 21 cm) lined with shredded wood bedding material. Food and water were available ad libitum. Water was supplied through a tube using an automated system that did not require bottle changes. Fresh food and clean cages were supplied once a week. Four litters, one from each pregnant rat, were culled to five males and five females per litter. Two litters were assigned to the EH group, and two litters were assigned to the MS group ($n = 10$ male pups per group). Behavioral effects were analyzed for both group effects and litter effects to ascertain that differences found were due to the experimental manipulation (MS or EH) as opposed to the litter that the subjects came from.

The subjects were weighed on postnatal day 2 (P2). MS or EH took place for 10 days total. On P2 through P6 and P9 through P13, the pups allocated to the MS and EH groups were removed from their mothers during the light phase, taken to a separate room, and placed together in a heated incubator to maintain body temperature. MS pups were separated for 6 h/day, while EH pups were removed from their mothers for a 15 min period. The subjects were not manipulated on P7 or P8. After P13, the pups were not separated again and stayed in their home cage with their respective dams until P21 when they were weaned. Each of the four litters was placed in a separate cage and was provided with free access to food and water.

In addition, 12 standard facility reared (SFR) P21 males were obtained from the same commercial supplier. These rats were used as SFR controls not subjected to MS or EH manipulations. From P21 until testing started on P28, all pups were handled daily for 5 min to habituate them to the experimenters. The Harlan facility at Houston provides similar rearing conditions to ours: shredded Aspen bedding in opaque polypropylene cages, cage changes only once a week while pups are nursing, and light cycle with lights on at 0600 h and off at 1700 h. Our lights were on at 0600 h and off at 1800 h, so the difference in light cycle between our two facilities was minimal. The 1-week adjustment period prior to testing should have been sufficient time to adapt to the extra hour of light.

2.2. Open-field (OF) and light–dark (LD) activity

All subjects were tested for OF activity during the first testing day (PND28), in the LD test the next day, and again in the OF test on the third day. All tests were 10 min in duration. The tests were conducted in an OF activity chamber (43 cm × 43 cm × 30.5 cm) (Med Associates, St. Albans, VT). The four lateral sides of the chamber were clear plastic, with a fiberglass white bottom. Activity was detected by arrays of infrared light beam motion detectors (16 × 16, 1 in. apart). One array of detectors was 1 cm above the floor, and another array 6 cm above the floor to detect rearing. The chambers were controlled by the Activity Monitor program, version 5.10 (Med Associates), which records various parameters related to the time course of the subject's behavior. The chambers were washed with a soapy solution between each session.

Using a modified setup of the OF activity chamber, we also performed a LD test (Takahashi et al., 1989). A dark compartment that covered half of the total area of the OF chamber was placed in the chamber dividing its total area in two compartments: an illuminated side and a dark side. The chamber included a small hole that allowed the subjects to move between the dark and light compartments of the chamber. Subjects started the test in the lighted compartment. The parameters measured in the OF and LD chamber are defined as follows.

2.2.1. Orienting behavior

Rearing consists of stopping ambulation and standing on the hindlimbs and is used as a measure of orienting behavior because orienting or non-selective attention is associated with the duration of a rat's rearing episode, where longer rearing indicates more orienting behavior (Aspide et al., 1998; Gallo et al., 2002).

Parameters related to orienting behavior:

(1) *Rearing counts*. Number of periods of continuous beam breaks reported by the upper array of beams.
(2) *Rearing duration*. Vertical time divided by vertical counts for each time bin.

2.2.2. Impulsive behavior

The first parameter that we used to index impulsive behavior was the speed of ambulation exhibited by rats from different groups. Bursts of fast ambulation would serve as an index of impulsivity analogous to what is observed in the impulsive/hyperactive type of ADHD (Gonzalez-Lima, 2005). The second measure was the relative time that the subjects spent in the center of the OF. Increased time in the periphery (thigmotaxic time) is associated with anxiety-like behavior, while time spent in the center puts the animal at risk (Clement et al., 1995). Rats normally prefer staying next to a wall where no predators

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