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Comparison of depressive behaviors induced by three stress paradigms in rats

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HIGHLIGHTS

- Different stressors may induce dissimilar depression subtypes.
- Difference in intersexual depression prevalence may be attributed to psychosocial factor.
- Individual difference is more obvious in desperation behaviors than that in anhedonia.

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ABSTRACT

Depression is a severe psychiatric disorder, which is a huge burden on both the individual and society as a whole. Neurobiological studies of depression on humans are limited by ethics. Animal models established by stressor stimulation are currently effective tools for the neurobiological study of depression. In this study, we comparatively analyzed behavioral heterogeneity, gender, and individual differences in animal models reflecting early life stress, adverse events in adulthood, or combined early life stress and stressful events in adulthood. Results demonstrated that these three different stressors induced dissimilar depressive behaviors. Maternal deprivation (MD) induced severe anhedonia. Chronic unpredictable stress (CUPS) induced the most severe decrease in desperation behavior, moderate anhedonia, and moderate loss of interest in exploration of the surroundings. Dural stress (DS) exposure caused the most severe decline in interest in exploring the surroundings. Male rats all exhibited some form of depressive behavior after they were exposed to MD, CUPS and DS. In contrast, no depressive performance was observed in female rats after they were exposed to MD, and the CUPS only decreased the total distance the rats crawled in the open field test. Rats exhibited more obvious individual differences in floating time than in the vertical activity, total distance and sucrose preference rate when experiencing stress. Our study suggests that different stressors may induce different depression subtypes and that the observed differences in the prevalence of depression between genders in the clinic may be due to effect of psychosocial factors which affects humans more strongly than rats. Our study also suggests that individual difference is more obvious in desperation behaviors than that in exploratory interest and anhedonia when the individual experienced stress.

1. Introduction

Depression is a psychiatric disorder characterized by heterogeneous symptoms and etiology [1]. Patients with depression also show divergent response to standard therapy with an estimated 40%–50% of patients showing little to no response to selective serotonin reuptake inhibitors (SSRIs) treatment [2]. The heterogeneity in the etiology of depression and clinical manifestations may suggest the existence of different subtypes of depression. Several neuroimaging studies have detected structural abnormalities in regions involved with HPA axis regulation in individuals that experienced both depression and early-life trauma, while individuals with depression alone did not. This may suggest the existence of structural differences in the brain of individuals suffering from different depression subtypes [3,4]. It is currently unclear whether the symptoms of depression and structural differences in the brain are associated with etiological heterogeneity. In addition, neurobiological studies in humans are extremely difficult to do and sometimes even impossible to do without violating ethics. Therefore, animal models are often used to study depression; however, it is impossible to establish a single animal model that is able to reflect the various subtypes of depression.

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Given the fact that environmental stress has been verified as one of the cardinal factors associated with the development of depression [5], animal models of depression are generally built upon exposing the animals to various chronic stressors that represent the stresses a patient with depression may face during early life or in adulthood. At present, a variety of depression animal models have been established. Among them, maternal deprivation (MD), chronic unpredictable stress (CUPS), and the combination of these two stresses (dual stress, DS) are the most commonly-used paradigms that induce depressive behaviors in rodents [6–8]. The MD, CUPS, and DS paradigms represent an early life stressful event, a stressful event during adulthood and the combination of these two stressful events, respectively. Therefore, these animal models reflect obvious heterogeneity in etiology [9]. However, no study has comparatively studied the differences between MD, CUPS and DS-induced depressive behaviors in rats. In addition, depression is more prevalent in women but current animal studies are often conducted in male rodents. In this study, we compared behavioral differences between rats under each of the three depressive animal models, behavioral differences between genders, and further analyzed individual differences.

2. Materials and methods

2.1. Animals and grouping

Ten male and 30 female Sprague–Dawley rats at 3 months old were provided by the Animal Center of Central South University and housed under standard conditions in accordance with the Guide for Care and Use of Laboratory Animals (Chinese Council). All experiments were conducted in accordance with an approved protocol from Central South University. Every effort was made to minimize animal use. One male was housed with 3 female rats. The female rats were checked every day for vaginal plug. The male rat was removed on the day a vaginal plug was found in the female rat. Rats were then checked at 9:00 every day for delivery after fertilization. Rat pups born before 9:00 were defined as postnatal day 1 (PND 1). Newborn offspring from 30 pregnant rats were mixed based on gender and randomly divided into eight groups: male and female maternal deprivation groups (MMD, N = 16; FMD, N = 17), male and female chronic unpredictable stress groups (MCUPS, N = 15; FCUPS, N = 11), male and female dual stress groups (MDS, N = 20; FDS, N = 10), and male and female control groups (MC, N = 15; FC, N = 15). MMD and FMD rats received maternal deprivation for 2 weeks after birth. MCUPS and FSUPS rats received chronic unpredictable stress for 3 weeks after reaching 10 weeks old. MDS and FDS rats first received maternal deprivation for 2 weeks after birth, and then received chronic unpredictable stress for 3 weeks after reaching 10 weeks old. MC and FC rats received only standard husbandry care.

2.2. Maternal deprivation (MD)

The MD paradigm was performed as previously described [10]. Briefly, rat pups were isolated from their mothers and littermates for 6 h daily from PND 1 to PND 13 (the isolation occurred at 9:00–15:00). To block communication between mothers and pups, each offspring was placed in a new cardboard box (32 cm × 32 cm × 14 cm, divided into four cells of the same size) covered with sawdust in a new room and later returned to their home cage when the experiment finished at 15:00. All experiments were performed in a temperature-controlled room (25 °C). After PND21, rats were randomly housed socially (5 rats per cage) with the same gender until adulthood (10 weeks).

Table 1
The procedure of chronic unpredictable stress.

	Week 1	Week 2	Week 3
Monday	Electric footshock	Cage tilting	Elevated platform
Tuesday	Cage tilting	Elevated platform	Food deprivation
Wednesday	Restraint	Electric footshock	Electric footshock
Thursday	Water deprivation	Food deprivation	Cage tilting
Friday	Elevated platform	Cage tilting	Water deprivation
Saturday	Food deprivation	Restraint	Restraint
Sunday	Restraint	Water deprivation	Elevated platform

2.3. Chronic unpredictable stress (CUPS)

The CUPS paradigm was performed according to a published protocol [11] with few modifications. Rats at 10 weeks old were randomly exposed to one of the following stressors once a day for 3 weeks: water deprivation for 24 h, food deprivation for 24 h, home cages tilted 30° Clockwise for 24 h [13], an elevated open platform (10 cm × 10 cm, 160 cm in height) for 2 h [12], electric foot shock for 20 s (800 mA, 1-s duration, average 1 shock/10 s) or restraint stress for 2 h [13]. A stressor was given at different times during the day to avoid predictability, and the procedures are provided in Table 1.

2.4. Dual stress

The DS paradigm was performed according to a published protocol [8]. Briefly, pups first received maternal deprivation for 2 weeks after birth and then received chronic unpredictable stress for 3 weeks after reaching 10 weeks old as described above.

2.5. Open field test

Open field test was performed as previously described [8]. The open field arena was made from an open rectangular plastic box (100 cm × 100 cm × 30 cm) with 25 squares (20 cm × 20 cm) painted on the floor. The 25 squares include 16 peripheral squares (along the wall of the box) and 9 central squares. At the time of the test, rats were marked by an investigator blind to the experimental design. Rats were then placed individually in the center of the field and allowed to explore the area freely for 5 min. The activity of the rats was recorded by an overhanging camera that was linked to a personal computer. Ethovision 3.0 (Noldus, The Netherlands) was used to track the behaviors of the rats. The total distance a rat crawled in the arena and the number of vertical activity the rat performed during the 5 min test were recorded and used for assessing the rats' interest in exploring their surroundings. The arena was cleaned with 70% alcohol between tests to ensure the current rat's behaviors are not affected by the imprint of previous rats. All behavioral tests were carried out on rats at the age of 13 weeks.

2.6. Forced swimming test

Forced swimming test was performed 24 h after open field test following a previously established protocol [14]. Two swimming sessions were conducted: a 15-min pretest on the first day followed by a 5-min test the next day. At the time of test, rats were placed individually in a Pyrex cylinder (21 cm × 46 cm) filled with 25 °C water to a depth of 30 cm. After swimming for 15 min on day 1, rats were dried with towels and placed back in their home cage. The cylinder was emptied and refilled with water between rats. Twenty-four hours after the first trial, rats were placed in the swimming apparatus again for a 5-min test. A video camera hung above the cylinders was used to record the rats' activity. The floating time (the time a rat spent in keeping its head above water with only slight movement) was used for assessing desperation behavior in rats. The data were analyzed by two researchers blind to the experimental design.

2.7. Sucrose consumption test

Sucrose consumption test was performed as previously described [15]. The whole test took 3 days. On day 1, rats were housed individually