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Research Report

Effects of social housing on hippocampal dendrites and behavior in ovariectomized rats

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ABSTRACT

Social stress is both species and gender specific. For female rats, individual housing and social instability housing conditions are associated with behavioral indicators of stress and depression. The present study directly compared the effects of six weeks of individual housing, social instability and mixed sex, semi-crowded housing in a visible burrow system (VBS) on ovariectomized female rats. Paired, stable housing was used as the control. Behavioral tests were conducted two, four and six weeks into the housing manipulations and included sucrose consumption, social interest, and activity in the open field. Following a series of four behavioral tests, animals were sacrificed and brains were processed for Golgi impregnation. Basal dendrites of CA3 hippocampal neurons were measured. Results indicate that the individual housing and social instability groups were comparable to the control group for all measures. In contrast, the rats housed in the VBS exhibited reduced activity in open field testing, and alterations in social interest. Dendritic lengths were also reduced in those animals living in the VBS in comparison to the animals housed in pairs. To our knowledge, this is the first report of behavioral and neural effects of VBS housing on female rats. Further research is necessary to determine what facets of the VBS housing are responsible for the behavioral and neural changes.

This article is part of a Special Issue entitled 'Animal Models'.

1. Introduction

Major Depressive Disorder is a global public health issue associated with decrements in physical health (Cassano and Fava, 2002; Moussavi et al., 2007). Although the etiology of depression is complex (Firk and Markus, 2007; Goldberg, 2006), there is now widespread agreement that chronic stress contributes to both behavioral changes and to functional alterations of the hippocampus and other limbic regions (Joëls et al., 2007; McEwen, 2007; Sapolsky, 2000).

The continued progress in research on the neurobiological bases of depression is dependent on the availability of valid, reliable, and relevant animal models (Matthews et al., 2005; Frazer and Morilak, 2005). Three such models which have yielded important results include the chronic mild stress (CMS) model (Baker et al., 2006; Willner, 2005; Willner et al., 1992), restraint stress (McLaughlin et al., 2005, 2007) and exposure to conspecific aggression such as that experienced in a visible burrow system (VBS) (Blanchard and Blanchard, 1990).

Deciding on an animal model must include consideration of gender. Because women are approximately twice as likely to experience depression as men (Ohayon, 2007), a female-specific model of depression is a priority. The etiology of depression for women is complex, with cultural, social, genetic and hormonal factors postulated to account for this gender disparity (Kessler, 2003; Kuehner, 2003). Thus developing a model with construct validity, i.e. one which "follows a plausible explanatory theory for the human condition" is essential (Dalla et al., 2010, p. 227).

Social stress therefore may be an especially valuable component of an animal model of depression. One form of social stress which is effective for female, but not male, rats is individual housing. Brown and Grunberg (1995) systematically compared corticosterone levels in female and male rats housed singly, in groups, or in crowded cages. Corticosterone levels, taken once after 14 days of this housing, were highest in male rats living in groups of ten under crowded conditions. In contrast, corticosterone levels were higher for the individually housed females compared to all of the grouped housing conditions, regardless of spatial density.

Social instability is another model of inducing depression-like responses in female rats. Haller et al. (1998) alternated housing gonadally intact female rats (oviducts were ligated to prevent pregnancy) between individual housing and crowded mixed sex housing. Instability was enhanced by changing the group membership each day. Control animals were stable male–female pairs.

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After 14 days, females living in the social instability condition showed chronic stress-related changes including reduced weight gain, thymus atrophy, adrenal hypertrophy and elevated plasma corticosterone levels. Further studies found that even without the male rats, this social instability paradigm resulted in a reduction in time spent in social behavior, an increase in time spent in aggressive behavior, and a reduction in preference for a sucrose solution and reduced food intake (Baranyi et al., 2005; Haller et al., 2004; Herzog et al., 2009).

While the social instability model has been effective in inducing behavioral and physiological changes in female rats, a well-documented social stress for male rats is the visible burrow system or VBS (Blanchard and Blanchard, 1990). The VBS consists of a large open field attached to smaller compartments interconnected by a tunnel system. When several males and females are housed together in the VBS, fighting among the males is initially high. Over time, this aggression subsides as one male achieves dominance. Behavioral, physiological, and neural effects of VBS housing on male rats have been reported (Blanchard and Blanchard, 1990; Blanchard et al., 1995, 2001b; Kozorovitskiy and Gould, 2004). An apparent advantage of this model is the semi-natural environment simulated by the VBS.

The present study was designed to determine the effectiveness of three types of social stress for inducing depression in female rats: individual housing (INDIV), social instability (INST) and mixed-sex semi-natural housing (VBS). The VBS model was chosen even though females do not develop the social hierarchies which underlie result in stress for males housed in this condition (Tamashiro et al., 2004). Nonetheless, there are reports that female rats living in the VBS are subjected to high levels of agonistic behaviors from both dominant and subordinate males (Blanchard et al., 2001a).

A paired housing control (CON) condition was used as the reference group. All animals were ovariectomized to control for hormone fluctuations across the estrous cycle. Exogenous estrogen was not provided since chronic treatment with estrogen induces receptivity in female rats (Davidson et al., 1968), which would be a confounding variable for those animals living in the VBS. We hypothesized that each of the experimental conditions of Individual Housing, Social Instability, and mixed-sex VBS housing would result in anhedonia, reduced social interest, low levels of exploration of the physical environment and retraction of dendrites of hippocampal CA3 neurons.

2. Materials and methods

2.1. Animals

Female Sprague-Dawley rats, bred in the vivarium and between 49 and 70 days of age, were anesthetized with ketamine (75 mg/kg)-xylazine (5 mg/kg), and bilaterally ovariectomized. After the surgery, animals were housed two per cage and allowed 14 days to recover before being randomly assigned to experimental groups. Body weights were taken each week. All animals were housed under a reversed light-dark cycle with the lights on 21:00–9:00 h.

2.2. Experimental conditions

Rats were randomly assigned to one of four housing conditions ($n = 8$ per condition). Shoe-box style polycarbonate cages were used for all animals except for those in the VBS. INDIV subjects were housed singly (33 cm × 30 cm × 18 cm) and CON animals were housed two per cage (50 cm × 38 cm × 21.5 cm). Animals assigned to the INST group alternated between individual and grouped housing phases. For the grouped housing period, the INST subject was introduced into socially established groups of three non-experimental, gonadally intact female rats (50 cm × 38 cm × 21.5 cm). After 24 h, they were returned to an individual cage for 24 h. Four different established groups were used and the INST animals were rotated through these groups.

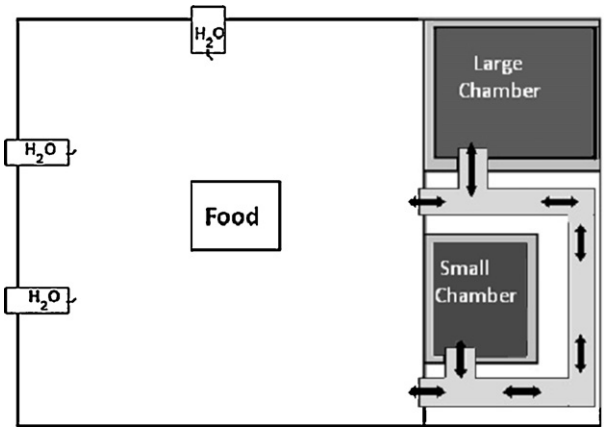

Fig. 1. Diagram of the VBS. The open space: 62 cm × 62 cm × 45 cm; tunnels: 9.5 cm H × 9.5 cm W; darkened chambers: 25 cm × 21 cm × 18.5 cm and 17.5 cm × 14.5 cm × 18.5 cm. Food and water were constantly available.

A diagram of the VBS is shown in Fig. 1. A large open space contained food and water. This space was interconnected via clear tunnels to two smaller darkened chambers. The VBS housed four experimental females and four intact male rats of approximately the same age. The composition of each VBS was stable throughout the experimental period.

2.3. Behavioral tests

Four different behavioral tests were administered once per week for four weeks, beginning two weeks after animals were placed in experimental conditions. All behavioral experiments were performed under red lighting, between 1200 h and 1500 h. The timeline for all tests and experimental procedures is presented in Fig. 2.

2.3.1. Sucrose consumption tests

During the week prior to the start of behavioral testing, all animals were given three sucrose training sessions. Briefly, the animals were placed in individual cages with a bottle of 1% sucrose solution and given ad libitum access for 1 h before being returned to their home cage. Prior to the actual sucrose consumption tests, animals were water deprived for 12 h. At the beginning of the dark phase, they were placed in a clean individual cage and presented with a pre-weighed bottle of 1% sucrose solution. Following the 1 h test, the bottle was again weighed. The total amount of sucrose solution consumed, measured in grams, was recorded.

2.3.2. Open field tests

For the 10 min open field tests, rats were placed in a darkened open field apparatus (35.5 cm × 35.5 cm) and data were collected using an automated open-field locomotor activity apparatus (Digiscan, Omnitech Electronics, Columbus, OH). Activity measures recorded included the total moving time, total distance, time spent in the corners of the open field, and horizontal movements.

2.3.3. Social interest tests

For the social interest tests, the test rat was placed in a clear Plexiglas chamber (51.5 cm × 36.5 cm × 27 cm). Smaller chambers (18 cm × 11.5 cm × 16 cm) were affixed to either end of the main chamber and a 2.2 cm diameter hole was cut in the partition between the main chamber and the small chambers. For each test, an ovariectomized female rat was placed in one small chamber and an intact male was placed in the other, with the placement alternated each week.

The tests began when the experimental rat was placed in the large chamber and lasted for 10 min. Behaviors recorded during the test included the number and

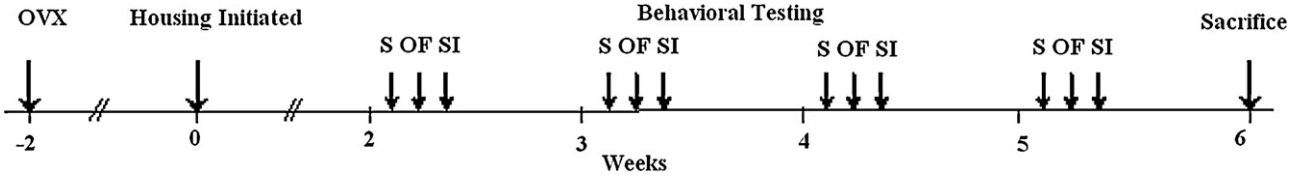

Fig. 2. Schedule of procedures. Ovx: ovariectomy; S: sucrose consumption tests; OF: open field tests; SI: social interest tests; Ex: exploration of novel objects tests.