Behavioural Brain Research 293 (2015) 208–216

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Environmental manipulation affects depressive-like behaviours in female Wistar-Kyoto rats

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HIGHLIGHTS

- Environmental enrichment reduces anhedonia in WKY and Wistar females.
- Social and physical isolation increases anhedonia in both strains.
- WKY females were significantly less active in both FST and EPM.
- The immediate environment may influence symptoms of depression and anxiety.

ARTICLE INFO

Article history:
Received 26 March 2015
Received in revised form 8 July 2015
Accepted 12 July 2015
Available online 26 July 2015

Keywords:
Environmental enrichment
Wistar-Kyoto
Depression
Anxiety
Sucrose preference
Isolation

ABSTRACT

While the efficacy of pharmacological interventions to treat depression has been well-studied in animal models, much less work has been done to shed light on how changes in the immediate environment can impact behaviour. Furthermore, most studies have focused on male rodents despite the prevalence of mood disorders in women. In this study, 36 Wistar Kyoto (validated animal model of depression) and 36 Wistar (control) female rats were used to examine the effects of environmental manipulation on depressive- and anxiety-like behaviours. Animals were assigned to one of three groups: standard (3 rats/cage), enriched (6 rats/cage plus physical enrichment), and isolation (1 rat/cage) housing. The elevated plus maze (EPM) and forced swim test (FST) were conducted prior to, and four weeks after environmental assignment to measure anxiety-like and depressive-like behaviours, respectively. Sucrose preference assessed anhedonia both before and after environmental assignment. Weight was measured every week to monitor weight-gain over time. Post-environment sucrose preference was significantly increased in animals in enriched housing as compared to those in isolated housing in both strains. While there were significant differences between strains in measures of open arm duration in the EPM and immobility in the FST, there appeared to be no differences between environmental groups. The results of this study highlight the importance of environmental factors in the expression of anhedonia. Enrichment appears to reduce anhedonia while isolation increases anhedonia. These effects should be studied further to assess whether longer periods of social and physical enrichment alleviate other symptoms of depression.

1. Introduction

Depression is one of the most prevalent mental health disorders in the world today and places an enormous burden on the economy and healthcare systems worldwide [13,33,64]. According to The Global Burden of Disease study started by the World Health Organization in 1990, major depressive disorder (MDD) has the largest global burden of disease of all the non-fatal neuropsychiatric disorders, and is predicted to become one of the top three burdens of disease along with HIV/AIDS and ischaemic heart disease by the year 2030 [44]. Major depression and anxiety disorders often show significant comorbidity [25]. While there is debate as to whether these are distinct or overlapping disorders, it is clear that the presence of anxiety disorders is one of the strongest risk factors for developing depression [27,46].

Women are diagnosed with MDD at roughly twice the rate of that observed in men [50,55]. In fact women have a 21% lifetime prevalence for a major depressive episode as compared to 13% of men [32]. The apparent gender differences in MDD worldwide have been attributed to an increased likelihood of sexual abuse in childhood [14], hormonal fluctuations associated with menstrual cycle, child bearing, and menopause [49], as well as greater genetic

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http://dx.doi.org/10.1016/j.bbr.2015.07.035

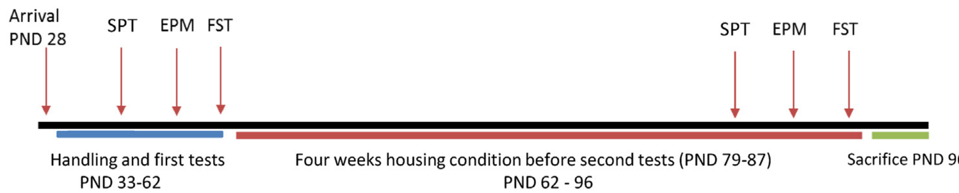

Fig. 1. Experimental timeline. PND: post natal day, FST: forced swim test, EPM: elevated plus maze and SPT: sucrose preference test.

vulnerability to stressful life events [31]. However, in studies that employ animal models of depression and anxiety, there exists a large male bias, again due to the hormonal fluctuations at play during the estrous cycle which cause significant changes in both physiology and behaviour (for review see [45]. Zucker and Beery [5,69] found that even in studies of diseases that predominantly affect women such as anxiety and depression, the research is primarily carried out with male animals.

The environment can also play a large role in the development of depression. There is an association between developing depression and the quality of the environment [21]. Socioeconomic status, stressful life events, social support, and physical exercise are many facets of the immediate environment that can affect well-being and in turn lead to depression and anxiety. There is much evidence to support the benefits of physical exercise [11,15,57], and social support [10,30,54] on mild to moderate depression in humans.

Environmental enrichment (EE) has been used as a way to incorporate both physical and social stimuli in animal models. In this paradigm, multiple animals are housed together in a large cage with novel stimuli changed every 2–6 days [59]. Studies utilizing EE have shown it to have an anti-depressant-like effect in rats by creating changes in both behaviour and neurophysiology. For instance, EE increases serotonin concentrations in the prefrontal cortex [8] and can ameliorate the effects of chronic stress by promoting cell survival and differentiation and increasing glucocorticoid receptor expression in the hippocampus [58,62,63]. Taken together, it appears that EE can exert not only a protective effect against multiple types of stressors (for review see [19] but can in some cases reverse the effects of these stressors altogether [16,20,47]. While pharmaceutical agents are often used to treat depression and anxiety, the current study aimed to explore whether environmental changes, without pharmaceutical manipulation, can have an impact on an established animal model of depression.

The Wistar Kyoto rat (WKY) was originally bred to be the control animal for the spontaneously hypertensive rat [51] but has more recently been used as a genetic model of depression [35], for review see Ref. [52]. The WKY rats show a combination of depressive- and anxiety-like behaviours as well as a marked decrease in locomotion and social withdrawal [48]. Because even pre-pubertal WKY animals exhibit both depressive and anxious symptoms, they are considered a model of childhood depression [40,42]. Furthermore, the depressive-like behaviour in WKY rats appears to be a model of treatment-resistant depression as these animals tend not to respond to selective serotonin reuptake inhibitors [36,38,60]. However, their depressive-like behaviours in the forced swim test (FST) do appear to be alleviated in response to low doses of ketamine [61], resveratol [29] and some tricylclic antidepressants and monoamine oxidase inhibitors [65]. Given what is known about the response of WKY rats to pharmaceuticals, it is surprising that there are no studies on the effects of environment on behaviour in the WKY rat.

This study examined whether changes to the environment can impact depressive- and anxiety-like behaviours in WKY and Wistar female rats. To our knowledge, this is the first study to examine the impact of environmental manipulation on behavioural measures observed in WKY female animals. Of particular interest was the question whether something as relatively 'mild' as an increase in social and physical stimuli through EE could have an effect on measures of anxiety and depression. Animals were randomly assigned to one of three environments—standard, enriched, or isolated. Depressive and anxiety-like behaviours were assessed using the FST and elevated plus maze (EPM), respectively for reviews of FST see Ref. [39] and EPM see Ref. [26]. Anhedonia was assessed through the use of the sucrose preference test. Weight and estrus cycle were monitored both before and after environmental assignment and analysed to explore whether the type of environment had an effect on both behavioural and physiological markers.

2. Materials and methods

2.1. Animals

A total of 36 Wistar and 36 Wistar Kyoto (WKY) female rats were obtained from a local supplier (Charles River Laboratories, Québec, Canada). All procedures were approved by the University of Ottawa Animal Care Committee. Due to space and time constraints, animals were acquired in two cohorts: a group of 18 Wistar and 18 WKY female rats were first tested and sacrificed, followed by a second identical cohort. Animals arrived to the facility at three to four weeks of age or post natal days (PND) 21–28 and were housed three per cage in standard housing conditions with a day/night cycle of 12 h:12 h and temperature of $21.5 \pm 1\,^{\circ}$C (humidity ~40%). Throughout the experiment, animals were provided with food and water ad libitum. They were allowed to acclimate to the home cage for 5–7 days and then were handled for five consecutive days. At PND 40, animals were acclimated to the taste of a 1% sucrose solution for five days. Sucrose was then withdrawn for three days and sucrose preference was assessed twice over the next four days. Behavioural testing commenced four days later to ensure that sucrose withdrawal would not affect their behaviour (for review on sucrose addiction see Ref. [2]). At PND 55, animals completed the EPM, and two days later the FST. The FST was carried out after the EPM as not to cause the animals undue stress. Animals were then randomly assigned to their housing condition at PND 62 and were kept there until sacrifice at PND 96. Combining both cohorts, there were six groups (three Wistar and three WKY) with 12 animals in each group. Animals in each strain were housed separately; in other words, Wistar-Kyoto animals were always housed only with other Wistar-Kyoto animals. Housing in the assigned conditions lasted for a period of four weeks before behavioural testing commenced. All animals were kept in their respective environment during the second set of tests to avoid the potential stress from switching environments. This is referred to as the post-environment test throughout the study. There was minimal interaction between investigators and animals during the four week period, apart from weekly cage and daily food/water changes. Animals were tested again following the environmental manipulation using the same behavioural measures as described above. Sucrose preference was assessed at PND 79 and 81 with EPM and FST at PND 85 and 87 respectively. See Fig. 1 for a diagram of the study timeline. Therefore, all rats were tested twice, once before assignment to their housing condition (pre-environment) and again four weeks following housing assignment