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Research report

Divergent effects of isolation rearing on prepulse inhibition, activity, anxiety and hippocampal-dependent memory in Roman high- and low-avoidance rats: A putative model of schizophrenia-relevant features

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HIGHLIGHTS

- Isolation rearing induces differential effects in RHA-I and RLA-I rats.
- Isolation rearing induces PPI deficits, hyperactivity and anxiety in RHA-I rats.
- Isolation rearing induces spatial reference memory deficits in RHA-I rats.
- Isolation rearing induces spatial working memory deficits in RLA-I rats.
- RHA-I rats may be a valid model for schizophrenia-relevant features.

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ABSTRACT

Social isolation of rats induces a constellation of behavioral alterations known as "isolation syndrome" that are consistent **with** some of the positive and cognitive symptoms observed in schizophrenic patients. In the present study we have assessed whether isolation rearing of inbred Roman high-avoidance (RHA-I) and Roman low-avoidance (RLA-I) strains can lead to the appearance of some of the key features of the "isolation syndrome", such as prepulse inhibition (PPI) deficits, increased anxious behavior, hyperactivity and memory/learning impairments. Compared to RLA-I rats, the results show that isolation rearing (IR) in RHA-I rats has a more profound impact, as they exhibit isolation-induced PPI deficits, increased anxiety, hyperactivity and long-term reference memory deficits, while isolated RLA-I rats only exhibit deficits in a spatial working memory task. These results give further support to the validity of RHA-I rats as a genetically-based model of schizophrenia relevant-symptoms.

1. Introduction

Isolation rearing (IR) has been used to induce detrimental effects on brain development and adult behavior which mimic some features or symptoms present in neurodevelopmental disorders, including schizophrenia. The alterations induced by IR are enduring, robust and replicable, which may allow a better understanding of the neurobiological disturbances causing a wide range of symptoms relevant to developmental psychiatric disorders like schizophrenia. This will also facilitate the discovery of new pharmacological targets with enhanced efficacy and less undesired effects [1]

A variety of behavioral abnormalities induced by IR have been reported (for a review see Ref. [1]). These behavioral changes are usually labeled as "isolation syndrome" and, according to Jones et al. [2] and Fone and Porkess [1] they include hyperactivity, neophobia,

Abbreviations: IR, Isolation rearing; RHA-I, Roman high-avoidance rats; RLA-I, Roman low-avoidance rats; PPI, Prepulse inhibition; MWM, Morris water maze.

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prepulse inhibition (PPI) deficits, cognitive/learning impairments and increased anxious and aggressive behaviors [1,3,4,5–7].

The Roman high-(RHA) and low-avoidance (RLA) rat lines/strains (depending on whether they are outbred – i.e., lines-, or inbred – i.e., strains-) have been selectively and bidirectionally bred for their rapid (RHA) vs. extremely poor (RLA) ability to acquire the two-way active avoidance task [8,9]. Extensive research conducted over near four decades has revealed that anxiety/fear and stress sensitivity are among the most prominent behavioral traits that distinguish the two Roman lines/strains [for review see Refs. 8,9]. Thus, compared to their RLA counterparts, RHA rats (both from the outbred line – RHA/Verh- or from the inbred strain – RHA-I-) show decreased unconditioned and conditioned anxiety/fear [e.g. Refs. 8,9,10,11,12,13], a proactive coping style [e.g. Refs. 13,14] and lowered activation of the hypothalamus–pituitary–adrenal (HPA) axis in response to stress [e.g. Refs. 13,14,15].

In Del Rio et al. [16] and Oliveras et al. [17] we proposed that the Roman high- and low-avoidance rat lines/strains could be a valid model of differential schizophrenia-related features. Thus, compared to RLA rats, RHAs show enhanced impulsive behavior in the 5-choice serial reaction time (5-CSRTT) and DRL-20 operant tasks [18–20], deficits in latent inhibition (in this case RHA-I rats were compared with Sprague Dawley rats[21]; and unpublished results from our laboratory), and impaired PPI and spatial working and reference memory [16,17,22,23–25]. Regarding the predictive and construct validity of the model, RHA rats show enhanced locomotor activity as well as mesolimbic dopaminergic sensitization to repeated (DAergic) psychostimulant administration [26–28], augmented mesocortical dopaminergic response to stress [29], increased stereotypic response to the dopamine agonist apomorphine [30–32] and neurochemical and neuromorphological evidence of decreased hippocampal function [33–35]. Furthermore, Klein et al. [20] showed that RHA-I had no detectable expression of mGluR2 in the frontal cortex, hippocampus and striatum, as well as increased fronto-cortical density of 5-HT2A receptors (for the implications of the mGluR2 in schizophrenia see Ref. [36]). Collectively these RHA vs RLA profiles suggest that (inbred and outbred) RHA rats may be a valid model of some behavioral and neurobiological features related with schizophrenia.

In the present study we evaluated the impact that IR has on prepulse inhibition (PPI) of startle, on anxiety in the elevated zero-maze, on locomotor activity in a new environment and on spatial working memory and long-term reference memory in the Morris water maze (MWM). We hypothesized that RHA-I rats will exhibit more profound and robust IR-induced deficits in these tasks than their RLA-I counterparts.

2. Methods

2.1. Subjects and housing

At postnatal day 21, male RHA-I rats (n = 36) and RLA-I (n = 40) were randomly assigned to one of the two housing conditions: in pairs (12 RHA-I rats and 16 RLA-I rats; in macrolon cages of 50 cm × 25 cm × 15 cm) or isolated (24 rats of each strain; in macrolon cages of 35 cm × 25 cm × 15 cm). Isolated rats had auditory, olfactory and visual but not physical contact with littermates. Rats from each experimental group came from 7 to 8 different litters. We included a greater number of rats in the isolated groups because preliminary PPI experiments (data not shown) suggested us that there could be larger variability as a consequence of IR treatment, and thus the increase in the number of animals in the IR groups might eventually reduce variability. All rats were reared and maintained in the same animal room, under a 12:12 h light-dark cycle (lights on at 08:00 a.m.), with controlled temperature (22 ± 2 °C) and humidity (50–70%) and with free access to food and water. After 14 weeks of isolation the experimental procedures began as described below, and the housing conditions were the same throughout the whole test battery. All experiments/tests were carried out during the light phase of the cycle. The experiments were approved by the committee of Ethics of the Autonomous University of Barcelona in accordance with the European Communities Council Directive (86/609/EEC) regarding the care and use of animals for experimental procedures.

2.2. PPI

After 14 weeks of isolation rats were submitted to PPI testing. Four startle boxes (SR-Lab Startle Response System, San Diego Inst., San Diego, USA) were used. They consist in a Plexiglas cylinder situated on the top of a platform with a sensor that detects changes in strength made by the movements of the rat in each trial. Auditory stimuli were delivered by two speakers situated 15 cm from each side of the cylinder. Each box is constantly lit by a 10 W lamp. The data are transduced by an accelerometer into a voltage and then saved into a computer for further analysis.

The startle session started with a 5 min habituation period in the startle chambers. Then, 10 “pulse-alone” trials (105 dB, 40 ms) are delivered in order to obtain a baseline measure of the startle response (Baseline 1). After this, each one of the 4 different types of trials (pulse-alone, prepulse-pulse and no stimulus trials) were randomly administered 10 times (40 trials in total): Pulse-alone trials (105 dB, 40 ms, Baseline 2, this was the variable used to calculate the %PPI; see the equation below); Prepulses of 59 dB and 63 dB (20 ms) followed by the pulse (105 dB, 40 ms), with an interstimulus interval of 100 ms; finally, 10 trials in which no stimulus was delivered and only the background noise was present (55 dB). At the end of the session, 5 “pulse-alone” trials were delivered to have a measure of habituation to the startle stimulus (Baseline 3). The interval between trials was 10–20 s with a mean of 15s. The maximal magnitude (i.e. the peak) of startle response was recorded during 200 ms after the onset of the pulse.

The percentage of PPI (%PPI) is calculated according to the formula: %PPI = 100 − ((startle amplitude on prepulse trials/startle amplitude on pulse trials) × 100)

2.3. Elevated zero-maze

Two weeks later (16 weeks of isolation), rats were tested in the elevated zero-maze. The maze, similar to that described by Shepherd et al. [37], is composed of an annular platform (i.e., a circular corridor 10 cm width and 105 cm diameter). The maze is made of black plywood and is elevated 65 cm above the ground level. It has two open sections (quadrants) and two enclosed ones (with walls 40 cm height).

The maze was placed in a room dimly illuminated by a red light. The trials were videotaped and the measures were taken outside the testing room by a trained observer. Trials began with the animals placed in the enclosed quadrant facing the wall.

The following variables were measured for 5 min (see Refs. [38,10]): time spent in open sections, number of entries into open sections, latency of the first entry to the open section, head dips through the edge of the open sections of the maze and line crossings among the eight different zones defined in the maze.

2.4. Locomotor activity

Two weeks later (18 weeks of isolation), rats were tested in the activity boxes to assess horizontal locomotor activity. The test was carried out in 3 identical Plexiglas activity cages (40 × 40 × 40 cm).