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Prepulse inhibition and latent inhibition deficits in Roman high-avoidance vs. Roman low-avoidance rats: Modeling schizophrenia-related features

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HIGHLIGHTS

- Roman High-Avoidance rats display prepulse inhibition deficit
- Roman High-Avoidance rats show latent inhibition deficit
- There is an association between prepulse inhibition and latent inhibition
- The Roman High-Avoidance rat strain presents schizophrenia-relevant features
- The Roman rats may model differential vulnerability to schizophrenia symptoms

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ABSTRACT

The aim of the present study was to obtain further evidence supporting the validity of a new genetically-based rat model for the study of schizophrenia-relevant symptoms. The Roman high- (RHA-I) and low-avoidance (RLA-I) inbred rats have been psychogenetically selected for their rapid versus extremely poor acquisition of the two-way avoidance task in the shuttle box and present two well-differentiated profiles regarding several traits related to anxiety, impulsivity and sensitivity to (dopaminergic) psychostimulants. In this study we have tested animals from both strains in two behavioral paradigms that are related to schizophrenia, i.e. prepulse inhibition (PPI) and latent inhibition (LI) of fear-potentiated startle (FPS). The results show that while RLA-I rats display good PPI and LI to the context, RHA-Is show an impairment of PPI and no sign of an LI effect, which goes in the direction of the results obtained in schizophrenic patients. Therefore, although further behavioral and psychopharmacological work needs to be done, the present findings and previous studies carried out in our laboratory and others allow us to propose the RHA-I rat strain as a putative genetic rat model of differential schizophrenia-related features.

1. Introduction

The inbred Roman high- and low-avoidance (RHA-I and RLA-I) rat strains were derived from the Swiss sublines (RHA/Verh and RLA/Verh), which have been psychogenetically selected since 1972 (Dr. Peter Driscoll, Institut fur Verhanstensbiologie, Zürich, Switzerland; Driscoll and Bättig, 1982) for their very good versus extremely poor acquisition of two-way active avoidance in the shuttle box [1,2]. These inbred strains have been maintained in our laboratory at the Autonomous University of Barcelona (Medical Psychology Unit, Dept. Psychiatry and Forensic Medicine, Autonomous University of Barcelona, Spain [2–4]) since 1996 and have been extensively characterized for behavioral and neurobiological phenotypes. A large amount of studies have been carried out with the Roman rat lines/strains (i.e. outbred or inbred, respectively) along the past four decades, and several traits have been seen to differ between these lines/strains, other than their differential ability to acquire the two-way avoidance task. For instance, RLA rats show higher signs of anxiety/fearfulness, increased hormonal stress responses (ACTH, corticosterone and prolactin secretion), better spatial reference learning/memory and spatial working memory than the RHAs [1,5–13].

Thus, RLA rats are anxious/fearful and show passive coping when facing conflict and/or stressful situations, whereas RHA rats are less anxious/fearful, display proactive coping responses, which in turn allow them to quickly acquire the two-way avoidance task [2,4,6,7,9–11,14].

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In contrast, RHA rats are considered to be novelty and substance seekers, presenting higher locomotor sensitization and meso-telencephalic dopaminergic activation than RLA rats when repeatedly treated with psychostimulants [15–17].

Impulsivity, or difficulty in controlling irrelevant responses, has been proven to be another feature of the RHA line/strain [18,19]. In this connection, since RHAs also have worsened learning-memory capacity (see references above), it has been hypothesized that this line/strain may have deficits in executive functions [20–22]. Likewise, RHA rats are impaired in sensorimotor gating processes, as shown by deficits in prepulse inhibition (PPI) of the startle response compared with RLAs [20,22]. Along with these profiles, the fact that RHA rats display enhanced dopaminergic responses and that hyperactivity of dopaminergic systems is a vulnerability factor for schizophrenia, prompted us to suggest that RHA rats could be a promising model of the disorder [20].

Schizophrenic patients show deficits in sensorimotor gating and attentional processes, like PPI and latent inhibition (LI), which are considered endophenotypes of the disorder. PPI reflects the ability of an acoustic prepulse of relatively low intensity to diminish the acoustic startle response (ASR) caused by a subsequent acoustic pulse of higher intensity. It is an operational measure of the pre-attentive filtering process known as sensorimotor gating, which refers to the neurological processes of filtering out redundant or unnecessary stimuli that take place in complex systems. It is a cross-species phenomenon that can be measured in both, mammals and humans, thus being a good paradigm for translational research [20,23–29]. The LI phenomenon refers to the retardation of associative learning between a conditioned stimulus (CS) and an unconditioned stimulus (US) resulting from pre-exposure to the CS alone prior to conditioning. Different cortical and sub cortical areas are involved in PPI regulation. There is evidence that OFC, AC, mPFC, hippocampus, VTA and BLA alterations have a modulatory effect on PPI, causing a reduction or even a disruption of it. Some studies have also suggested that modulation of both PPI and LI may share some limbic structures, including the hippocampus, the basolateral amygdala and the nucleus accumbens, which support the hypothesis that both processes may be related [30,31].

Thus, a rat model of schizophrenia-related features with good validity would be expected to present impairments of both PPI and LI [32]. In a preliminary study from our laboratory we observed that RHA-I rats had some deficits in latent inhibition of the two-way avoidance response in comparison with Sprague-Dawley rats [33], but RHAs could not be compared with RLA-I rats due to the incapability of the latter to acquire the two-way avoidance task. Therefore, in the present study we aimed at measuring LI in a task that could allow direct comparison between both the RHA-I and RLA-I strains, i.e. LI of fear-potentiated startle (FPS; [30,34]. In the procedure of fear-potentiated startle (FPS), animals are submitted to a classical conditioning training by performing several pairings of a neutral stimulus (the prospective CS) with an aversive one (US, electric footshock). Once this is done, when the CS is presented, the acoustic startling stimulus (pulse) elicits a bigger startle response - ASR - in the rat, i.e. the subject shows greater ASR following "CS-pulse" presentation than following "pulse alone" presentation. Pre-exposure of rats to the prospective CS (prior to classical conditioning training) produces the LI phenomenon, i.e. a decrease of ASR following "CS-pulse" presentation due to a decrease of the strength of the classical conditioning association [30,34].

We hypothesized that, relative to RLA-Is, RHA-I rats would display PPI and LI impairments.

2. Material and methods

2.1. Subjects

A total of 42 male Roman high-avoidance (RHA-I) and 42 male Roman low-avoidance (RLA-I) rats were used in this study. All rats came from the breeding colony of inbred Roman strains established in our lab (Dept. Psychiatry and Forensic Medicine, Autonomous University of Barcelona) in 1996. At the beginning of the experiment the animals were experimentally naive (they had not been used in any other experimental or testing procedure), they were approximately 5 months old, weighing 410.3 ± 7.0 g (RHA-I) and 412.8 ± 8.8 g (RLA-I) (means ± sem).

Rats were housed in pairs of the same sex and strain in macrolon cages (50 × 25 × 14 cm) and maintained with food and water ad libitum under standard conditions of temperature (22 ± 2 °C), humidity (50–70%) and a 12 h light-dark cycle (lights on at 08:30 h).

The experiments were carried out during the light phase of the cycle (from 9:00 to 19:30 h) and the procedures were approved by the Ethics Committee of the Autonomous University of Barcelona in accordance with the European Communities Council Directive (86/609/EEC) on the use of laboratory animals.

2.2. Apparatus

2.2.1. Prepulse inhibition and latent inhibition

The prepulse inhibition (PPI) and latent inhibition (LI) tests were conducted in four identical acoustically-isolated boxes of 90 × 55 × 60 cm (Sr-Lab Startle Response System, San Diego Inst., San Diego, USA). Each box consists of a plexiglas tube/cylinder (8.2 cm × 25 cm) where the rat is placed, situated on top of a platform with a sensor that detects the strength caused by the movements of the rat when it is subjected to the acoustic stimulus (startle response). These data are transduced by an accelerometer into a voltage which is amplified, digitized and saved into a computer for further analysis. A white noise generator provides background noise of 55 dB through a speaker located on the roof of the chamber, while two other speakers in both sides of the cylinder produced the acoustic stimuli (prepulse and pulse).

There was a constant light in the chamber during the procedure of the PPI which came from a 10 W lamp. The light used as conditioned stimulus (CS) in the LI procedure came from a different lamp located on the roof.

2.3. Procedures

2.3.1. Test for prepulse inhibition (PPI)

The animals were individually placed in the plexiglas tube and had 5 min of habituation to the conditions of the startle box (the cylinder and the chamber). Background noise of 55 dB was constantly present. Then a baseline acoustic startle response (ASR) measure was obtained by administering 10 pulses of 105 dB and 40 ms (BL1, baseline 1). After that, different types of trials were repeated 10 times. These trials were presented in blocks of 6 in a pseudorandom order:

- "Pulse-alone" trials of 105 dB (these were considered as the second "baseline" ASR measure - BL2, used to calculate the % prepulse inhibition – %PPI; see below).
- Prepulses of 65, 70, 75, and 80 dB (20 ms) followed by the startle stimulus (i.e. the pulse of 105 dB, 40 ms), with an inter-stimulus interval of 100 ms.
- Trials with no stimulus (just the background noise of 55 dB).

These trials were given with an inter-stimulus interval of 15 s on average, with a range of 10–20 s. The performance (i.e. the startle response) of the rat was recorded during 200 ms following the presentation of the 105 dB pulse.

At the end of these 60 trials (i.e. the 10 repetitions of the 6-trial blocks), another baseline ASR was measured by administering 5 pulses of 105 dB (BL3) in order to compare with the previous baselines (BL1 and BL2) to see whether there had been a habituation process or not. The %PPI for each prepulse intensity was calculated by applying the