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Association between prepulse inhibition of the startle response and latent inhibition of two-way avoidance acquisition: A study with heterogeneous NIH-HS rats

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HIGHLIGHTS

- Prepulse inhibition and latent inhibition have been tested in outbred NIH-HS rats.
- The NIH-HS rat population shows relatively good prepulse inhibition.
- The NIH-HS rat population displays wide variability of prepulse inhibition scores.
- Prepulse inhibition scores positively predict the level of latent inhibition.

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ABSTRACT

This study presents the first evaluation of the associations between responses in two paradigms related to schizophrenia in the genetically heterogeneous NIH-HS rat stock. NIH-HS rats are a stock of genetically heterogeneous animals that have been derived from eight different inbred strains. A rotational breeding schedule has been followed for more than eighty generations, leading to a high level of genetic recombination that makes the NIH-HS rats a unique tool for studying the genetic basis of (biological, behavioral, disease-related) complex traits. Previous work has dealt with the characterization of coping styles, cognitive and anxiety/fear-related profiles of NIH-HS rats. In the present study we have completed their characterization in two behavioral models, prepulse inhibition (PPI) and latent inhibition (LI) of the two-way active avoidance response, that appear to be related to schizophrenia or to schizophrenia-relevant symptoms. We have found that these rats display PPI for each of the four prepulse intensities tested, allowing their stratification in *high*, *medium* and *low* PPI subgroups. When testing these three subgroups for LI of two-way active avoidance acquisition it has been observed that the *LowPPI* and *MediumPPI* subgroups present impaired LI, which, along with the fact that the *HighPPI* group presents significant LI, allows us to hypothesize that responses in these two paradigms are somehow related and that selection of NIH-HS rats for *Low* vs *HighPPI* could make a promising animal model for the study of clusters of schizophrenia-relevant symptoms and their underlying neurobiological mechanisms.

1. Introduction

Animal models of schizophrenia-relevant features are important to improve our knowledge on the relationships among neurobehavioral mechanisms and particular symptoms of the disorder. The complexity and diversity of schizophrenia does not allow to focus on the entire constellation of symptoms, just as schizophrenic patients do not manifest every possible symptom. Some of the most commonly used animal analogues reproduce positive (psychotic) and some negative symptoms of schizophrenia through administration of dopamine agonists, serotonin agonists or glutamate antagonists. These drug effects, and their antagonism by typical (dopamine-2 receptor antagonists) or atypical (serotonin 5-HT2A antagonists, and some glutamate receptor agonists) antipsychotic drugs, have led to the three main neurochemical hypotheses of the disorder, i.e. dopaminergic, serotoninergic and glutamatergic hypotheses [1–4].

Other rodent analogues of schizophrenia-related features focus on modeling negative (e.g. impaired social behavior) or cognitive (e.g. impairments of spatial learning, working memory) symptoms of the disorder, as well as sensorimotor gating or attention-related processes which are found to be impaired in schizophrenic patients [5,6]. Two of these processes are the prepulse inhibition of the acoustic startle

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response (PPI) and latent inhibition (LI). 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 [5–12]. 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. Like PPI, LI has also been shown to be impaired in schizophrenic patients [12–16]. It has been assumed that deficient PPI and LI in schizophrenia reflect dysfunctions in pre-attentional and/or cognitive filter mechanisms of the brain [7,9,13,14,17,18]. Thus, the assessment of sensorimotor gating and attentional filtering in animal models has increasingly become an important tool for the understanding of the neurobiological basis of the disorder and the development of novel drugs with improved efficacy [6,9]. Several studies have been carried out to unravel the neural basis and structures involved in both PPI and LI processes. In the case of the PPI, Koch and Schnitzler [19] proposed that the ASR is triggered by excitatory input from the auditory pathway to the midbrain inferior colliculus (IC). In turn, IC activates the superior colliculus (SC), with important projections to the pedunculopontine tegmental nucleus (PPTg) that inhibits the pontine reticular nucleus (PnC). The PnC regulates the activity of motor neurons and the motor response. The inhibition of the PnC leads to a downregulation of the startle response, resulting in the measurable PPI effect [11,19,20]. Importantly, however, cortical and limbic areas, such as the orbitofrontal cortex, anterior cingulate, medial prefrontal cortex, nucleus accumbens, basolateral amygdala, and the hippocampus are known to modulate PPI or to affect its regulation in different ways, as reflected by disruption of PPI following manipulations of these structures (for review see [11,19]). Likewise, the brain circuitry regulating LI appears to involve structures like the entorhinal cortex, the basolateral amygdala, the hippocampus or the nucleus accumbens [18,21]. The fact that some brain structures modulate both processes lends support to the idea that they might be somehow related at the neurobiological level.

In this context, associations between PPI and LI have been found in some selectively-bred rat strains (e.g. APO-SUS and APO-UNSUS rats, RHA-I and RLA-I rats), but not in other cases of either genetically-selected or outbred rats (e.g. see review by Del Río et al. [12]). This scenario makes it still more relevant to systematically evaluate whether associations between PPI and LI exist in unselected outbred rats, as this might shed some light on putative shared mechanisms between both processes.

Hansen and Spuhler [22] developed a genetically heterogeneous rat stock, the National Institutes of Health – N/Nih – Genetically Heterogeneous Rat Stock (NIH-HS rats) through the crossing of 8 parental inbred rat strains (as much separated as possible). A rotational breeding schedule has been followed for more than 80 generations, generating a genetic recombination pattern that has been shown to deliver ultra-high resolution for genetic mapping studies of complex traits [23,24]. The fact that each of these rats represents a singular genetic mosaic of the parental haplotypes makes them a unique tool for studying the genetic basis of biological, behavioral and disease-related complex traits. Thus, several studies have been carried out in order to characterize these heterogeneous rats, including profiles of timidity and defensive flight [25], coping styles and stress hormone responses [26,27], levels of unlearned anxiety and learned fear [28,29], as well as high-resolution genetic mapping of quantitative trait loci (QTL) to identify genes contributing to fear/anxiety-related behaviors [23,24] multiple sclerosis [24,30], bone fragility [31–33] and other disease-related complex traits [30,34,35].

The present study was devoted to characterize, for the first time, the associations between PPI and LI in genetically heterogeneous NIH-HS rats. Our interest in the measurement of the PPI and LI in NIH-HS rats arises, as said earlier, from the fact that these processes seem to be impaired in schizophrenia. This study may provide indications on whether selection (i.e. stratification) based on "normal" PPI variation can be a useful rat model for studying clusters of schizophrenia-relevant symptoms.

We hypothesized that if PPI and LI processes are both affected in schizophrenia and share some common underlying mechanisms, then we would expect that animals that exhibit deficits of PPI would also show impaired LI.

2. Materials and methods

2.1. Animals

The subjects of this study have been 107 NIH-HS rats with an average age of 3–4 months at the beginning of the experiment (weight, 330 ± 9.8 g, mean ± SEM). They were housed in pairs of the same sex and family in macrolon cages (50 × 25 × 14 cm) and maintained with food and tap water ad libitum. These animals are bred and grown at the Autonomous University of Barcelona (UAB) and kept in standard conditions of temperature (22 ± 2°; 50–70% relative humidity) and a 12 h light–dark cycle (lights on at 08:30 h).

The NIH-HS rat stock was derived from 8 inbred rat strains by Hansen and Spuhler [22]. These 8 parental strains were the MR/N, WN/N and WKY/N (whose ancestors trace back to the original Wistar stock), the M520/N and F344/N (established in the 1920s with an unknown origin), the M520/N and the ACI/N (hybrids between the August and Copenhagen stocks, the BN/SsN (derived from a color mutant from a stock of wild rats kept at the Wistar Institute), and the BUF/N strain [22,36]. To establish our colony, we received 40 pairs of NIH-HS rats from Dr. Eva Redei (Center for Comparative Medicine, Northwestern University, Chicago, USA) in 2004.

Tests were performed under the light phase of the cycle and all the protocols 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. Apparatus and procedure

2.2.1. Prepulse inhibition

Four acoustically isolated boxes of 90 × 55 × 60 cm were used (Sr-Lab Startle Response System, San Diego Inst., San Diego, USA). Each box consists of a plexiglas tube (8.2 × 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. The boxes are constantly lit by a 10 W lamp and the acoustic stimuli are delivered by two speakers placed 15 cm from each side of the plexiglas tube. A white noise generator provides background noise.

The startle session started with 5 min of habituation to the box. Then, 10 "pulse-alone" trials with the startle stimulus (105 dB, 40 ms) were administered to obtain a basal measure of the ASR (BAS1). After this, the different types of trials were randomly administered in blocks of 6 trials that were repeated 10 times (60 trials in total):

- "Pulse-alone" trials (105 dB), that constitutes the BAS2 measure used to calculate the percentage of PPI (see formula below).
- Prepulses of 65, 70, 75, and 80 dB (20 ms) followed by the startle stimulus (105 dB, 40 ms). These trials are "PPI" trials used to calculate the percentage of PPI (see formula below).
- Trials with no stimulus (only the background noise of 55 dB).

Following these 10 repetitions of 6 trials (60 trials), 5 "pulse-alone" trials were administered, this making the BAS3 measure.