Original research

Sensorimotor gating deficit in a developmental model of schizophrenia in male Wistar rats

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Abstract: ***Background:*** Isolation rearing is a neurodevelopmental manipulation that produces behavioral alterations in rodents that in many ways are consistent with resemble schizophrenia. Alteration in sensorimotor gating function has been seen in post-weaning social isolation rearing model of schizophrenia. Pre pulse inhibition (PPI) response is one of the reliable tests for investigation of sensorimotor gating deficits. Genetically variation has been seen in PPI test in rodent models of schizophrenia. The aim of this study is to investigate the sensorimotor deficit in developmental models of schizophrenia in male Wistar rats.

Method: Male Wistar rats (25 days old) were randomly allocated to isolated and social experimental groups. Isolated rats were kept individually per cage, while in social groups 3-4 rats were housed in each cage for eight weeks. On the eighth week sensorimotor deficit was determined in both social and isolated groups via PPI test. Three different pulse intensities were used as pre-pulse. PPI data were analyzed via repeated measures ANOVA across startle and pre-pulse intensities. One-way ANOVA was performed for each of the pre-pulse intensities followed by Tukey post-hoc.

Results: Isolation-reared rats showed sensorimotor gating deficits, reflected by decreased pre-pulse inhibition of the startle response compared with social rats ($P<0.0001$). This difference was observed in all three different intensities.

Conclusion: According to the results, we concluded that isolation rearing constitutes a valuable, noninvasive manipulation for modeling schizophrenia-like deficits in male rats.

Keyword: Schizophrenia; sensory gating; genetic; models, animal; developmental disabilities developmental model

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1. Introduction

Schizophrenia is a mental disorder characterized by abnormalities in thought processes and typical emotional responses. The symptoms of schizophrenia start typically in young adulthood with a prevalence about 1% in human societies. It is a major cause of disability and has great human and economic cost (1). Several mechanisms are involved in causing schizophrenia. On this basis, several animal models have been used to investigate the involved mechanisms. These animal models are categorized in four classes including pharmacological models, lesion models, genetic models and developmental models. Pharmacological models have been the most widely used models, which involve the manipulation of various neurotransmitters like GABA, glutamate, serotonin and dopamine. Dopamine seems to be the most important neurotransmitter involved and animal models for schizophrenia were first produced by altering the dopaminergic system. Lesion models are based on theories that introduce schizophrenia as a neurodegenerative model. In this type of models an area of the animal's brain is damaged. Developmental models are based on the epidemiological studies, which have shown that environmental factors during gestation or around childbirth increase the probability of showing schizophrenia's symptoms (2). Rodent social isolation model is one of the accepted developmental models. In this model the pups, which are kept

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in separate cages after being weaned, show positive symptoms of schizophrenia such as neophobia, a larger response to new stimulus, locomotor hyperactivity and increased aggression (3). Animals used as models for schizophrenia include rats, mice, and primates. In the rodent model of schizophrenia sensorimotor gating is disturbed. Pre-pulse inhibition (PPI) test, which is a diagnostic test in schizophrenia condition shows sensorimotor gating abnormalities (4, 5). PPI is a neurological phenomenon in which a weaker pre-stimulus (prepulse) inhibits the reaction of an organism to a subsequent strong startling stimulus (pulse). The reduction of the amplitude of startle reflects the ability of the nervous system to temporarily adapt to a strong sensory stimulus when a preceding weaker signal is given to warn the organism (5). PPI is detected in numerous species ranging from mouse to human. Strain-dependent differences in PPI disruption has been reported in different rat strains. Alkondon et al. reported that August Copenhagen Irish (ACI) rats are more sensitive than Sprague-Dawley rats to apomorphin-induced PPI disruption (6). ACI strain rats display a higher degree of excitation related to glutamatergic neurons. Glutamatergic system disrupts PPI in laboratory animals (7). It seems that in ACI rats, the glutamatergic interneurons in CA1 area of hippocampus are more active. This hyperexcitability of the CA1 area may contribute to the inhibition of CA1 pyramidal neurons and consequently decrease the glutamatergic hippocampal stimulation of the nucleus accumbens (6). This difference in PPI results has also been reported in pharmacologically induced schizophrenia in rodents. Faraday et al. reported that administration of nicotine for 14 days will reduce acoustic startle reflex and impair pre-pulse inhibition of startle in male and female Long-Evans rats but not in male Sprague-Dawley rats. He suggested that the effect of nicotine in sensory gating depends on genotype of the rats (8). Based on this information, the present study was designed to investigate the changes in pre-pulse inhibition test in socially isolated Wistar rats eight weeks after isolation.

2. Method

2.1. Animal

Rats of Wistar strain were supplied by the university animal house. Male and female rats were mated and after detecting the vaginal plaque the pregnant rats were placed in individual cages. The 23 day-old male pups were obtained from the breeding program and were randomly allocated to socially reared (3-4 rats/cage; n=9) or socially isolated (one rat/cage; n=9) rat groups. Rats were maintained in this situation for 8 weeks. The rats had free access to food and water at all times except during testing. Animals were reared in an environment with a temperature of 22.0± 2.0 degrees Celsius and 12 hours light/dark cycle. The animals in both groups experienced minimal handling and no environmental enrichment. The bed was changed once a week trying not to touch the animals. The socially reared and socially isolated rats did not differ significantly with respect to weight. All behavioral testing was conducted during a similar time of day between 10 to 12 AM.

Animals were treated in accordance with the standard guidelines for use of laboratory animals in research. All experiments were approved by the Institutional Animal Care and Use Committee.

2.2. Study design

Eight weeks after dividing the pups into the isolation or socially reared groups, rats were tested for acoustic startle/pre-pulse inhibition. In pre-pulse inhibition test a weaker acoustic pre-stimulus (pre-pulse) inhibits the reaction of animals to a strong acoustic startling stimulus (pulse). In this test, the ability of the nervous system for adaptation against a strong sensory stimulus is monitored through the reduction of the amplitude of a startle when a preceding weaker stimulus is applied for warning the animal. Testing apparatus consisted of a chamber in which the animal holder plate is mounted on a startle platform. The chamber was well-ventilated and suitable for rats weighing 200-300 gr. Acoustic stimuli were generated by speakers located at the back. The chamber was connected to a computer system to run the software. The startle reaction of the rat generated a pressure on the response platform and analogical signals were amplified, digitized, and analyzed by the computer software.

2.3. Pre-pulse inhibition session

For pre-pulse inhibition test, the rats were placed in the startle cages for a 5-minute acclimatization period. During this adaptation period a background noise of 65 db was applied. After this period, they were presented with 52 acoustic trials in a series of five different trials as follows: The pulse-alone trials (14 trials), the prepulse-pulse trials [30 trials (3×10 trials) with different prepulse-pulse trials] and the pre-pulse trials (8 trials), including four trials in the beginning and four trials at the end with the pulse intensity of 120 db, which were not included in the calculation of PPI percentage. In pulse-alone trials the intensity of pulse was set at 120 db with the duration of 4 msec. This period served only to accommodate the animals to the sudden change in stimulus conditions. In prepulse-pulse trials the pulse and pre-pulse periods were set at 100 milliseconds and 20 milliseconds, respectively. Time interval between the pulse and pre-pulse was set as 100 milliseconds and the pre-pulse was presented immediately before the startle pulse. Three different pre-pulse intensities (3, 6

and 12 db above background noise) were used. The intensity of pre-pulse in the pre-pulse trials was set at 65 db. PPI data are reported as percentage and calculated as below:

$$PPI = \frac{100 - [(prepulse + pulse) \times 100}{pulse}$$

2.4. Statistics

The results are reported as mean ± SEM. PPI data are reported as percentage. Comparison between social and isolated animals was done using one-way ANOVA followed by the Tukey test. P<0.05 was considered to be statistically significant.

3. Result

The results of PPI test in the social and isolated groups showed that PPI test is completely affected by the caring methods. In the PPI test, the isolated animals showed a significant reduction in PPI test comparing to social groups (Figure 1). Mean PPI was 32.3 ±1.5 percent in the social animals, which was significantly higher than the PPI of the isolated animals [F (1, 31) = 171.8, p < 0.0001]. Mean PPI was 11.9±1.3 percent in socially isolated animals.

This significant difference between the isolated and social groups was observed in different pre-pulse intensities. The percentages of PPI in social animals exposed to pre-pulse with the intensities of 3, 6 and 12 db were 20.0±2.0, 32.0±2.6 and 44.0±3.0 percent, respectively, which was higher than the background noise (p<0.0001). Isolated animals showed lower percentage of PPI in all pre-pulses used in this experiment. The percentage of PPI in isolated animals exposed to noises with 3, 6 and 12 db was higher than the background noise, as the pre-pulse, were 5.5±0.8, 10.2±0.8 and 20.1±1.1 percent, respectively. Significant difference exists between the isolated and social groups in all three pre-pulse intensities used in this experiment (p<0.0001) (Figure 2).

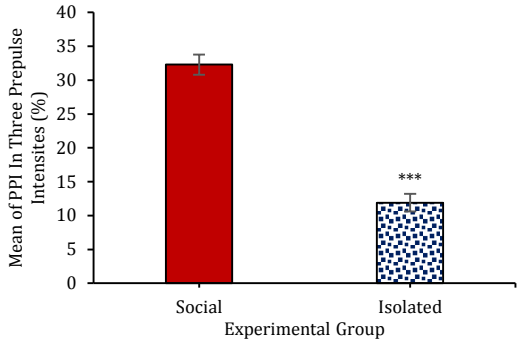

Figure 1: The effect of eight weeks of post-weaning social isolation on pre-pulse inhibition deficits in male Wistar rats. ***: P<0.0001

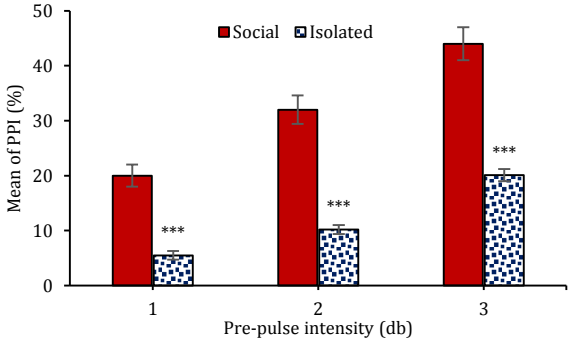

Figure 2: The effect of administrating different pre-pulse intensities on PPI deficit in social and isolated groups. Star shows the significant differences between social and isolated groups. ***: P<0.0001

4. Discussion

The startle reflex is a response to sudden relatively intense stimuli and is usually classified as a defensive response. Pre-pulse inhibition test is a form of startle reflex, which is widely used in rodents and is based on the normal suppression of the startle reflex when the intense startling stimulus is preceded by a weak pre-stimulus (9). The results of this study confirm that rearing Wistar rats in isolation for eight weeks after weaning results in deficit in PPI test, which is the indication of abnormalities in brain structure. This result is in accordance with the results reported in Suarez et al. study. The results of their study showed that Wistar albino rats that underwent 5 weeks of isolation rearing showed a marked increase in total horizontal locomotor activity and aggressive behaviors, which are similar to the positive symptoms seen in schizophrenia (10).

PPI test is a result of several conceptually important forms of behavioral plasticity but even these more complex processes exhibit striking similarities across species (11). PPI test has been explained as a reliable test to measure sensorimotor gating (12). PPI is considered an index of a centrally mediated inhibitory mechanism, which regulates sensory, motor and cognitive behaviors (13). We found a decrease in the percentage of PPI in all three pre-pulse intensities used, but the results showed an increase in the magnitude of the percentage of startle response when the intensity of the pre-pulse increased. Previous studies have reported very heterogeneous results in different animal models and humans in this respect. Whereas some studies have reported a decrease

in the test results (14), others have reported the contrary (15).

Sex and strain of the animals are two important factors, which should be considered when developmental animal models are used to investigate PPI alteration in psychological disorders (16). In this regard, Alkondon et al. reported higher levels of glutamatergic activity in the hippocampus of ACI rats compared with Sprague-Dawley rats. They believe that this difference could explain the strain-specific sensitivities to psychological models –induced PPI disruption (6). Interestingly, difference in PPI test results among different strains is more obvious when weak pre-pulses are used. Bullock et al. have begun to study inheritance patterns of PPI characteristics in mice. In these preliminary studies, PPI was compared among seven mice strains, and the strains with the highest and lowest levels of PPI were inbred. A quantitative analysis of inheritance revealed that PPI, but not startle amplitude per se, followed a pattern consistent with dominant transmission (17).

In rodents, PPI deficits can be induced by dopamine agonists such as apomorphine, and recent studies have identified heritable differences in the dopaminergic regulation of PPI in both mice (18) and rats (19). For example, Sprague-Dawley rats from Harlan Laboratories are significantly more sensitive to the PPI-disruptive effects of dopamine agonists such as apomorphin, compared to Long-Evans rats from the same Laboratories (19). These differences have been shown to be innate and neurochemically specific, and cannot be explained by differences in maternal behavior (20). Conceivably, this heritable strain difference in the "disruptability" of PPI may provide a useful model for understanding the basis for heritable differences in PPI in schizophrenia syndrome (21). Rat strain differences in sensorimotor gating might reflect genetic or epigenetic influences on a number of different biological systems, and many such differences undoubtedly arise from mechanisms with little relevance to the genesis of neuropsychiatric disorders. The specific strain differences described in these studies have been pursued experimentally from the levels of possible fostering effects and maternal-pup interactions, to different parametric behavioral manipulations, through possible pharmacodynamic mediators, neurochemical and neuroanatomical substrates, and more recently to regionally specific signal transduction mechanisms and gene expression (22).

5. Conclusion:

In summary, the aim of this study was to investigate the existence of impairments in PPI after eight weeks of post-weaning isolation in Wistar rats. We found that eight weeks of isolation decreased the PPI percentage, which indicates a poor inhibitory control and poor response to threatening stimulus. Based on the results presented herein, socially isolated Wistar rats are a good model for investigating the pathophysiology of schizophrenia and developing new drugs to treat the disease. These findings provide further validation for the social isolation model of impaired sensorimotor gating in schizophrenia, which is also detected across multiple sensory modalities.

6. Acknowledgment

None.

7. Conflict of interest

No conflict of interest was declared.

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9. Author contribution

FN and AS provided the concept and designed the project. AS and MM analyzed the data. MM provided data collection and FN managed the project and wrote the paper. All authors critically revised the manuscript and approved final version of the paper to be published. They agreed to be accountable for all aspects of the work.

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