Behavioural Brain Research 298 (2016) 310–317

Contents lists available at ScienceDirect

Behavioural Brain Research

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

Research report

Alterations to prepulse inhibition magnitude and latency in adult rats following neonatal treatment with domoic acid and social isolation rearing

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HIGHLIGHTS

- Adults rats were assessed following neonatal DOM treatment and/or isolation rearing.
- Social isolation lowered PPI amplitude in male rats.
- DOM treatment made rats refractory to isolation-induced PPI amplitude deficits.
- Isolation rearing and DOM produced an additive decrease in PPI latency.
- PPI amplitude and latency are dissociable and differentially affected by DOM and isolation.

ARTICLE INFO

Article history:
Received 30 March 2015
Received in revised form 5 November 2015
Accepted 9 November 2015
Available online 15 November 2015

Keywords:
Prepulse inhibition
Domoic acid
Isolation rearing
Animal models
Schizophrenia
Neurodevelopmental disorders

ABSTRACT

Deficits in perceptual, informational, and attentional processing are consistently identified as a core feature in schizophrenia and related neuropsychiatric disorders. Neonatal injections of low doses of the AMPA/kainate agonist domoic acid (DOM) have previously been shown to alter various aspects of perceptual and attentional processing in adult rats. The current study investigated the effects of combined neonatal DOM treatment with isolation rearing on prepulse inhibition behaviour and relevant neurochemical measures, to assess the usefulness of these paradigms in modeling neurodevelopmental disorders. Daily subcutaneous injections of DOM (20 μg/kg) or saline were administered to male and female rat pups from postnatal days (PND) 8–14. After weaning, rats were either housed alone or in groups of 4. Both the magnitude and latency of prepulse inhibition were determined in adulthood (approximately 4.5 months of age) and post-mortem brain tissue was assayed using Western blot. Social isolation alone significantly lowered PPI magnitude in male (but not female) rats while DOM treatment appeared to make animals refractory to this effect. Combining social isolation and DOM treatment caused an additive decrease in PPI startle latency. No statistically significant differences were found in the expression of D1, D2, TH, GAD65 or GAD67 protein in either the prefrontal cortex or hippocampus, although some tendencies toward differences were noted. We conclude that both neonatal low-dose DOM and social isolation affect prepulse inhibition in rats but that each paradigm exerts these effects through different neuronal signalling systems.

1. Introduction

Changes to perceptual, informational, and attentional processing are found in a number of human neuropsychiatric disorders including schizophrenia [1–3]. Characterized by impairments in the perception of reality, schizophrenia is diagnosed by some combination of positive, negative and cognitive symptoms [4]. Found in approximately 1% of the general population, schizophrenia results in great emotional cost to those directly affected, as well as large financial cost to the economy worldwide [5,6].

Believed to arise due to a combination of genetic susceptibility and environmental influence [7], schizophrenia manifests great variability in symptom profiles, developmental timecourse and response to treatment [8]. While past research has identified a number of associated genetic linkages, developmental risk factors, and neurobiological elements, the highly complex and heterogeneous nature of schizophrenia has presented significant challenges

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http://dx.doi.org/10.1016/j.bbr.2015.11.009
0166-4328/

for understanding the mechanisms of the disorder, as well as the development of successful treatments. Historically, treatment has focused primarily on the positive symptoms of schizophrenia. More recently, however, it has been suggested that a failure to reduce the processing of irrelevant incoming information (originally classified as a cognitive symptom) results in such information being afforded undue attention. Improper processing of incoming information may then result in the development of positive symptoms. It has, therefore, been hypothesized that the positive symptoms of schizophrenia may actually be a consequence of various information processing impairments such as those illustrated by disrupted prepulse inhibition (PPI) in both patients and animal models [9–12].

Prepulse inhibition is a measure of perceptual processing whereby there is normal suppression of the startle reflex when the startling stimulus is preceded by a less intense, non-startling stimulus [13]. This measure of sensory-motor gating is believed to be controlled by structures located in the lower brainstem and mediated by input from the forebrain [14]. A behaviour that is seen in many different species including rats and humans, PPI is reliably disrupted in a variety of neuropsychiatric disorders [15–17]. Assessments of prepulse inhibition are widely used in studies of the neural alterations of neuropsychiatric disorders, in the search for useful animal models, and in the preclinical evaluation of potential therapeutic agents [18–23].

Alterations in both dopaminergic [24,25] and GABAergic [26–29] signalling have been linked to altered PPI in rodents and to the clinical profile of schizophrenia. Historically, dopamine (DA) was the first neurotransmitter system to be implicated in schizophrenia, with the predominant hypothesis at the time being that symptoms of the disorder were caused by excessive DA transmission in the forebrain [30]. More recently, alterations to a variety of GABA system markers have been found in the post-mortem brains of people with schizophrenia, particularly in the hippocampus [31,32]. These changes include decreased somatostatin and parvalbumin containing interneurons, as well as decreases in glutamic acid decarboxylase (GAD) [33]. While the role of GABA in PPI has not been investigated as extensively as the role of DA, studies have suggested that this system plays an important role in PPI behaviour, particularly within the hippocampus and the nucleus accumbens (NAc) [26–29].

Past efforts to model disorders like schizophrenia in animals have employed various chemical and/or environmental challenges in rodents. Among these are a model developed in our laboratories, low-dose neonatal domoic acid (DOM) administration, and a well-established environmental challenge, social isolation rearing. In rats, injections of low-dose DOM throughout the second postnatal week results in later-onset changes in behaviours consistent with both the clinical presentation of schizophrenia and other animal models of the disorder including altered responses to novelty and reward seeking [34,35], changes in cognitive functioning [36–38], altered social interaction [39], and changes in stress response [40]. Many of these changes could be interpreted in the context of alterations in perceptual, informational, and attentional processing. Indeed, we have previously reported that neonatal DOM treatment results in a decrease in latent inhibition (a measure of attentional processing) and decreased PPI magnitude (a measure of perceptual processing) in adulthood [41–43] as well as select changes in proteins associated with the DA and GABA systems, particularly within the hippocampus, prefrontal cortex (PFC) and NAc [38,40,44].

In contrast to pharmacological manipulation of brain development, a number of studies have examined the role of early life stressors and/or environmental conditions on measures of perceptual, informational and attentional processing. One such condition is social isolation rearing. Since Hatch et al. [45] first reported that housing rats in isolation produced abnormal behavioural reactivity, many studies have shown that rats who experience social isolation (housed one animal per cage for some period of time post-weaning, still in auditory, visual and olfactory contact with other animals) display a variety of profound behavioural, neurobiological and neuroanatomical differences when compared to those rats who are raised in groups [46–50]. Of particular relevance to the current study are a number of reports that post-weaning social isolation housing disrupts PPI, although the presence and extent of the disruption may be affected by a variety of factors including the length of isolation, housing conditions, the strain used, and previous experience with behavioural testing [51–59]. Further, both the DA and GABA systems are believed to be affected by social isolation rearing, although results have been varied and often contradictory [60–63]

While most previous studies have used only one experimental intervention, attention has turned to the possibility of developing animal models that incorporate what has come to be referred to as a "multi-hit" approach. In the current study we have chosen to investigate such a multi-hit approach by combining the aforementioned established, but seemingly very different postnatal interventions that have previously been linked to both persistent changes in PPI and the expression of DA and GABA system proteins in adulthood; namely, neonatal administration of low-dose DOM and social isolation rearing.

2. Materials and methods

2.1. Experimental animals and injection procedure

Experimental animals, born in-house from 10 untimed pregnant Sprague-Dawley rats (Charles River Laboratories, PQ, Canada) were culled to 10-12 pups with an even number of males and females where possible. The day of parturition was designated postnatal day (PND) 0. On PND 7 pups were randomly assigned to either the DOM treatment group or the saline control group and ear-notched for identification purposes. From PND 8–14, pups were weighed and given a single daily subcutaneous (s.c.) injection of 20 μg/kg DOM (BioVectra DCL, PE, Canada) or saline.

On PND 21 rats were weighed, weaned and randomly assigned to either the isolation housing condition (1 rat per cage) or the group housing condition (4 rats per cage) with both sexes and drug groups equally represented in each housing condition. All animals were kept in solid bottomed cages that measured approximately 48 cm long × 24 cm wide × 20 cm deep for isolation housed rats, and 48 cm long × 38 cm wide × 20 cm deep for group housed rats. Animals who were group housed were placed with non-littermates of the same sex and drug treatment. All cages were placed in the same colony room so that isolation housed animals could still see, hear and smell other rats without having physical contact. This resulted in 4 treatment groups for both males and females: Saline treated/ Group housed (SG), DOM treated/Group housed (DG), Saline treated/Single housed (SS) and DOM treated/Single housed (DS). All rats ($n = 94$) received *ad libitum* access to food and water and were left undisturbed until behavioural testing began in adulthood (4.5 months of age). Rats were previously tested for latent inhibition (see [43]) at approximately 3.5 months of age before being used in this study. Animals were maintained on a reversed 12:12 h light-dark cycle with testing conducted during the dark phase. All procedures were conducted experimenter blind, run according to the guidelines established by the Canadian Council on Animal Care, and were approved by the Animal Care Committee at the University of Prince Edward Island.

2.2. Prepulse inhibition

2.2.1. Prepulse inhibition protocol

All animals (n = 11–12 per group) were weighed the day before PPI testing began. The startle apparatus (SR-Lab, San Diego Instruments, CA, USA) consisted of a clear tube that held the rat over