Neuroscience Letters 578 (2014) 22–26

Contents lists available at ScienceDirect

Neuroscience Letters

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

Neonatal domoic acid abolishes latent inhibition in male but not female rats and has differential interactions with social isolation

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HIGHLIGHTS

- Latent inhibition was measured in male and female rats following neonatal drug and/or isolation housing.
- Neonatal injections of low dose domoic acid abolished LI in adult male rats but did not alter LI in females.
- Social isolation rearing also reduced LI in male rats but not females.
- Drug treatment and housing condition had differing effects of LI at 48 h and 7 days post-conditioning.
- We conclude the mechanisms of LI disruption by DOM or isolation housing may be different as well as sex-specific.

ARTICLE INFO

Article history:
Received 3 January 2014
Received in revised form 20 May 2014
Accepted 11 June 2014
Available online 19 June 2014

Keywords:
Latent inhibition
Attentional processing
Domoic acid
Isolation rearing
Schizophrenia
Animal models

ABSTRACT

Deficits in attention have long been identified as a core feature in schizophrenia and related neuropsychiatric disorders. We have investigated the combined effects of neonatal treatment with domoic acid (DOM) and social isolation rearing (both putative animal models of schizophrenia) on latent inhibition (LI), a measure of attentional processing. Daily subcutaneous injections of 20 μg/kg DOM or saline were administered to rat pups from postnatal days (PND) 8–14. After weaning, rats were housed either alone or in groups of 4 until LI was assessed at PND 110 using a lick-suppression conditional emotional response paradigm. Neonatal treatment with DOM abolished LI behaviour in adult male rats regardless of housing condition when tested 48 h after conditioning, but this effect was not observed in female rats. Social isolation rearing also reduced LI in male rats, but not to the same extent as DOM. When tested again one week later, single-housed males treated with DOM displayed significant LI whereas saline treated or group-housed DOM males did not. No significant differences were found with females 1 week later. We conclude that neonatal DOM and social isolation both impair attentional processing in young adult male, but not female, rats although the mechanisms by which this occurs appear to be different.

1. Introduction

Deficits in attention have long been identified as a core feature in schizophrenia and related neuropsychiatric disorders [1]. Characterized by impairments in the perception and expression of reality, schizophrenia is a heterogeneous disorder comprised of some combination of positive, negative and cognitive symptoms [2]. The development of positive symptoms may be due, at least in part, to an inability to reduce the processing of irrelevant incoming information [3]. Latent inhibition (LI) is a normal cognitive process whereby previous non-reinforced experience with a particular stimulus impairs the ability of that stimulus to subsequently enter into new associations. According to Lubow [4] when a conditioned stimulus (CS) is followed by no consequence, the animal learns to ignore that stimulus. As a result, during later pairing of the CS with an unconditioned stimulus (US) the animal fails to attend to the CS and associative learning is impaired. This view of LI as learned inattention presents it as an adaptive mechanism, important for the proper processing of incoming stimuli [5].

Observed across many different species, including rats and humans, LI is reliably disrupted in humans with schizophrenia [6] and has become widely used in studies of the neural alterations in schizophrenia as well as in animal models of the disorder [4,7]. It has further been suggested that different aspects of the

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http://dx.doi.org/10.1016/j.neulet.2014.06.025
0304-3940/

LI changes observed in both clinical populations and animal models might illustrated different aspects and symptom categories of schizophrenia [8,9]. Disruption of LI is caused by a failure to inhibit attention to irrelevant stimuli. This behaviour would theoretically result in abnormally increased salience perception and distractibility, potentially leading to psychotic symptoms and therefore the positive symptoms of schizophrenia. However, abnormally persistent LI is caused by a failure to re-deploy attention when previously irrelevant stimuli becomes relevant again. This indicates cognitive inflexibility and impairment in attentional shifting which are associated with the negative and cognitive symptoms of schizophrenia [9].

We have previously reported that administration of low, subconvulsant doses (20 μg/kg) of domoic acid (DOM) (a kainate receptor agonist) to neonatal rats during a critical period of development [10], results in later-onset changes in behaviours consistent with both clinical schizophrenia and other animal models of the disorder. To date we have shown that DOM administered throughout the second postnatal week produces deficits in prepulse inhibition [11,12], altered responses to novelty and reward [13], changes in cognitive functioning [14,15] and altered social interaction [16]. Many of these changes could be interpreted in the context of alterations to attentional processing. Indeed we recently reported that LI was impaired in DOM treated rats when assessed using a conditioned taste aversion test [11].

In rodents, disruptions of LI can be achieved using chemical, surgical and environmental interventions including social isolation (for a review of factors affecting LI see [4]), although results reported following social isolation indicate that the effects may vary according to the timing of both the isolation and the testing, as well as the rat strain used [17–20]. Of particular relevance to the current study, Feldon et al. [21] found that rats raised in isolation after weaning may or may not display altered LI, depending on the extent of pre-weaning handling. These latter data indicate that the effects of isolation rearing on LI may be subject to interactions with other life experiences and highlight the possibility of using such "2-hit" models (combining a neonatal insult with an additional insult later in life) to better model neuropsychiatric disorders. Moreover both clinical [22,23] and experimental [24] data indicate that sex differences are important variables in both the origins and symptom profiles of psychiatric disease. Sex differences have also been previously reported in both the neonatal DOM model [11–16] and in social isolation models [20], so although most previous literature has reported data generated exclusively in male rats, it is becoming increasingly common to use both male and female rats when investigating animal models of disease or evaluating new therapies.

The current study was designed to further investigate the combined effects of neonatal DOM treatment and social isolation rearing on LI in both male and female rats using a conditioned emotional response task.

2. Materials and methods

2.1. Experimental animals and injection procedure

Rats were born in-house from 10 untimed pregnant Sprague-Dawley dams obtained from Charles River Laboratories (St. Constant, Quebec, Canada). The day of parturition was designated PND 0. Within 24 h of birth, litters were culled to 10–12 pups with an even number of males and females where possible. 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 to 14, pups were weighed and given a single daily subcutaneous injection of 20 μg/kg of DOM (BioVectra DCL, Charlottetown, PE, Canada) or saline.

On PND 21 rats were weighed, weaned and randomly assigned to either isolation housing (one rat per cage) or group housing (4 rats per cage), with both sexes and drug groups equally represented in each housing condition. This resulted in 4 treatment groups for both males and females: Saline/Group housed (SG), DOM/Group housed (DG), Saline/Single housed (SS) and DOM/Single housed (DS). Group housed rats were placed with rats that were not littermates but were of the same sex and drug treatment. All cages were placed in the same colony room so isolation housed animals could still see, hear and smell other rats, without having physical contact. All rats ($n = 94$) were maintained on a reversed 12:12 h light–dark cycle, received ad libitum access to food and water (except during behavioural testing as described below) and were left undisturbed until behavioural testing began in adulthood (PND 110). All procedures were conducted experimenter blind, 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. Latent inhibition

Latent inhibition was assessed using a conditioned emotional response task, adapted from Weiner and Arad [9]. The testing apparatus consisted of a standard rat operant chamber (Med-Associates, St. Albans, VT) with a grid floor, tone-generating speaker and a retractable drinking tube equipped with a lickometer. Prior to testing each animal was randomly assigned to either the pre-exposure (PE) or non pre-exposure (NPE) group, with both sexes and all treatment groups equally represented ($n = 6$ animals per group).

The LI procedure is outlined in Table 1. Each rat was tested twice; once at 48 h after conditioning (Test 1) and again one week later (Test 2). The time to complete licks 80–100 (before tone)(A) and licks 100–120 (tone on)(B) was recorded and used to calculate the lick suppression ratio using the formula $A/(A+B)$. A score of 0.003 indicates maximum drinking suppression and a score of 0.5 indicates no drinking suppression. Following testing, animals were returned to their homecages and the water restriction was ended. The presence of LI was indicated by the PE and NPE animals in a given treatment group (SG, SS, DG or DS) displaying significantly different lick suppression ratios during the testing phases.

2.3. Data analysis

Data were analyzed by 3-way ANOVA (drug treatment × housing condition × LI group) with repeated measures (test) where appropriate (SPSS Version 19). Post-hoc comparisons were conducted using Bonferroni t-tests with Levene's test for equality of variance. A result of $p < 0.05$ indicated significance. Values in text are expressed as mean ± SEM. Because of baseline differences observed in the amount of liquid consumed in the homecage (data not shown), as well as previous findings of LI differences between sexes [11], all LI data for males and females was analyzed separately.

3. Results

3.1. Pre-test performance measures

No significant differences in any variable were found in either sex when measuring the average number of licks taken or the latency to begin drinking during lick training or during rebaseline. An analysis of the amount of water consumed by each rat after being replaced in the homecage following testing revealed no significant effects in any variable, in either sex, during training days, conditioning days, or rebaseline days. A significant effect for housing was seen in males on the pre-exposure day [$F(1,39) = 5.392$,