Pharmacology, Biochemistry and Behavior 103 (2012) 338–344

Contents lists available at SciVerse ScienceDirect

Pharmacology, Biochemistry and Behavior

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

Neonatal domoic acid treatment produces alterations to prepulse inhibition and latent inhibition in adult rats

Amber L. Marriott [a], Catherine L. Ryan [b], Tracy A. Doucette [a,*]

[a] Department of Biology, University of Prince Edward Island, 550 University Avenue, PE, Canada, C1A 4P3
[b] Department of Psychology, University of Prince Edward Island, 550 University Avenue, PE, Canada, C1A 4P3

ARTICLE INFO

Article history:
Received 6 July 2011
Received in revised form 20 August 2012
Accepted 25 August 2012
Available online 7 September 2012

Keywords:
Domoic acid
Glutamate
Schizophrenia
Prepulse inhibition
Latent inhibition
Animal models

ABSTRACT

Schizophrenia is a complex and severe mental disorder characterized by positive, negative and cognitive symptoms. Characteristic behavioral alterations reflecting these categories of symptoms have been observed in many animal models of this disorder, and are consistent with those manifested in the clinical population. The purpose of this study was to determine whether early alterations in glutamate signaling would result in alterations to prepulse inhibition (PPI) and latent inhibition (LI); two assessments used for evaluating putative novel animal models with relevance to schizophrenia. In the present experiment, daily subcutaneous (s.c.) injections of 20 μg/kg of domoic acid (DOM) were administered to rat pups from postnatal days (PND) 8–14. When tested as adults, DOM treated rats displayed deficits in PPI that were dependant on both sex and time of day. No differences in startle amplitude, habituation, or movement were found during any test, indicating that the PPI deficits seen could not be attributed to baseline startle differences. Deficits in LI were also apparent when adult rats were tested using a conditioned taste aversion task, with DOM-treated animals displaying a significantly suppressed LI. These results suggest that early treatment with DOM may serve as a useful tool to model schizophrenia which in turn may lead to a better understanding of the contribution of glutamate, and in particular, kainate receptors, to the development and/or manifestation of schizophrenia or schizophrenia-like symptoms in the clinical population.

1. Introduction

Animal models provide one of the best ways to study the underlying neurobiological mechanisms that contribute to human disorders such as schizophrenia. Currently, there are a number of well established animal models with relevance to schizophrenia including neurodevelopmental lesion-based models (e.g. Lipska et al., 1993, 1995), genetically based models (e.g. Egan et al., 2001; Millar et al., 2000; Stefansson et al., 2002; Straub et al., 2002), prenatal-immune challenge models (e.g. Zuckerman and Weiner, 2003), and drug induced models (e.g. Gambill and Kornetsky, 1976; Sams-Dodd, 1997). All of these models illustrate an important aspect of schizophrenia and all display validity, but the type and degree vary widely with each different model. Because schizophrenia is a heterogeneous disorder, composed of some combination of positive, negative and cognitive symptoms (DSM-IV-TR, 2000), no single "ideal" animal model can represent the entire population of schizophrenic patients. Rather, as pointed out by Powell and Miyakawa (2006), it is critical that novel models be discovered so that each new model might represent a subpopulation, or particular aspect or endophenotype.

Issues of validity are always important to consider with respect to the development of any animal model. Understanding the validity of an animal model provides critical information about the strengths, uses and limits of the model in question (Geyer and Markou, 2000). Many animal models of schizophrenia seek, at least initially, to simulate the disease in terms of core behavioral symptoms, attempting to achieve face validity. This can be difficult to accomplish in an animal model of a complex human disorder such as schizophrenia, with the difficulty being further compounded by the fact that symptoms of the disorder vary widely between those affected. However, success in modeling certain symptoms of schizophrenia has been achieved using tests of behaviors that can be measured both in humans and rodent models. Prepulse inhibition (PPI) of the acoustic startle response and latent inhibition (LI) are two such behavioral measures which test for well known cognitive symptoms of schizophrenia (for reviews see Lubow, 2005; Swerdlow and Geyer, 1998; Swerdlow et al., 2000; Van den Buuse et al., 2005). Prepulse inhibition is the normal suppression of the startle reflex that occurs when the startling stimulus is preceded by a less intense, non-startling stimulus (Graham, 1975). 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 (Weiss and Feldon, 2001). Latent inhibition is the process by which

* Corresponding author at: Department of Biology, University of Prince Edward Island, 550 University Avenue, Charlottetown, PE, Canada, C1A 4P3. Tel.: +1 902 566 6055; fax: +1 902 566 0740.
E-mail address: tdoucette@upei.ca (T.A. Doucette).

0091-3057/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pbb.2012.08.022

pre-exposure to a stimulus without consequence inhibits the learning of later conditioned associations with that stimulus. Latent inhibition is considered to be a measure of ability to ignore irrelevant stimuli and allocate appropriate mental resources (Lubow, 1989). Observed across many different species, including rats and humans, PPI and LI are reliably disrupted in humans with schizophrenia (Baruch et al., 1988; Braff et al., 1978) and have become widely used in studies of the neural alterations of schizophrenia as well as in the search for useful animal models of the disorder (Ellenbroek et al., 1996; Grecksch et al., 1999; Zuckerman and Weiner, 2003).

Recent hypotheses propose that the neuropathology of schizophrenia is the result of an altered interaction between glutamate (Glu) and dopamine (DA) systems, with one of the most common theories being that hypofunction of the Glu system (particularly within the prefrontal cortex) results in hyperactivity of the mesolimbic DA neurons (Coyle, 2006). Contributions of early Glu dysfunction to schizophrenia have historically focused primarily on NMDA receptors (Bickel and Javitt, 2009; du Bois and Huang, 2007; Harris et al., 2003). More recently, however, the contribution of other Glu receptors to the pathophysiological manifestation of this disease has been explored. In particular, it would appear that kainate receptors, a subtype of ionotropic Glu receptor, may play a role in the etiology of schizophrenia and/or the manifestation of schizophrenia-relevant behaviors (see Meador-Woodruff and Healy, 2000 for review). It has also been shown that KA receptors play a modulatory role in the release of DA in the prefrontal cortex (Jedema and Moghddam, 1996; Wu et al., 2002). Behaviorally, Howland et al. (2004) demonstrated that an acute neonatal i.p. injection of kainic acid (1.5 mg/kg) administered on postnatal day (PND) 7 produced a significant deficit in prepulse inhibition (PPI) during early adulthood, but not during adolescence. Additionally, rats who received the kainic acid treatment displayed significantly higher spontaneous locomotor activity in response to amphetamine when compared to controls.

To date, research in our lab has focused on how the administration of low, sub-convulsant doses of domoic acid (DOM) (i.e. a kainate receptor agonist) (Verdoorn et al., 1991, 1994) to neonatal rats during a critical period of CNS development (Dobbing and Smart, 1974), affects behavior in adulthood. We have shown that DOM (20 μg/kg), administered daily during postnatal days 8–14, produces deficits in PPI (Adams et al., 2008a) and increases in responses to novelty (Burt et al., 2008a), a behavior believed to reflect signs of psychomotor agitation (Powell and Miyakawa, 2006). Other previously published results from our laboratory indicate that this early DOM exposure paradigm produces changes in cognitive functioning and alterations in the functioning of the mesocorticolimbic pathway (Adams et al., 2009; Burt et al., 2008b; Doucette et al., 2007). Taken together, this pattern of anomalies is consistent with clinical manifestations of schizophrenia and also with changes seen in current animal models of the disorder.

The purpose of the present study was to further explore the behavioral changes produced by early DOM exposure in two key behavioral paradigms; PPI and LI. This study characterizes these effects in order to address issues of face validity and to determine the potential usefulness of early DOM treatment as a neurodevelopmental animal model of schizophrenia.

2. Methods

2.1. Experimental animals and injection procedure

Experimental animals were the offspring of 10 untimed pregnant Sprague–Dawley rats 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 pups with an even number of males and females where possible, providing an average n of 8 for LI testing (with no group having an n below 7) and an average n of 12 for PPI testing (with no group having an n below 11), as a greater number of experimental groups are required for LI testing (pre-exposure, non pre-exposure, control) as compared to PPI (dark phase, light phase). The same animals were used for both behavioral tests, with pups from every litter being used in each treatment group for LI and pups from 5 litters used for each PPI experiment (dark vs. light phase). From PND 8–14, pups were weighed, marked with non-toxic marker for identification purposes and given a single daily subcutaneous injection of either saline or 20 μg/kg of DOM (obtained from BioVectra DCL, Charlottetown, PE, Canada). Rats were weaned on PND 21 and group housed (2–3 animals per cage) with non-littermates of the same sex and from the same treatment group. All rats received ad libitum access to food and water (except during LI testing, as indicated below). Animals were maintained on a reversed 12:12 h light–dark cycle (lights off at 7:00, on at 19:00). behavioral testing began when the animals reached PND 90. All parts of this study were conducted experimenter blind and according to the guidelines established by the Canadian Council on Animal Care and in accordance with the Animal Care Committee at the University of Prince Edward Island.

2.2. Preweaning assessments and weight

To ensure that the treatment procedure did not produce overt signs of toxicity, developmental measures were assessed beginning on PND 8. For eye-opening (defined as a break in the suture of both eyes) and auditory startle (defined as a visible startle to the noise made by a clicker held 10–15 cm above the pup's head), animals were tested until criterion was reached. Weight gain was also measured at various stages of development (PND 8–14, 20 and 89).

2.3. Prepulse inhibition

Animals were tested during either the light (21:00–5:00, n = 49) or dark (between 9:00 and 17:00, n = 51) phase of the light–dark cycle, as time of day has been reported as a biological factor which may affect PPI (Adams et al., 2008b; Chabot and Taylor, 1992; Frankland and Ralph, 1995; Swerdlow and Geyer, 1998).

The startle apparatus was an SR-Lab from San Diego Instruments (San Diego, CA, United States). Full details for PPI testing can be found in Adams et al. (2008b). In brief, all animals received a 5 minute acclimation period to the chamber before the experiment began, followed by 3 blocks of trials. The intertrial interval for all trials was an average of 15 s (ranging from 10 to 20 s) and a background white noise level of 70 dB was maintained. Average startle amplitude was obtained by measuring every 1 ms for 100 ms after the onset of the startle pulse, with startle amplitude defined as the average of the 100 readings.

Block 1 consisted of 6 120 dB white noise startle pulses, each 40 ms in length. These trials were used to normalize startle, to measure initial startle (pulse 1) and to establish a startle baseline for the beginning of testing (the average of pulses 2–6). Block 3 consisted of 5 120 dB white noise startle pulses, each 40 ms in length. These trials were used to establish a startle baseline for the end of the session (the average of the 5 pulses). Together, data from Blocks 1 and 3 were used to determine if there was any difference between the two groups in their startle amplitudes independent of PPI, as well as to measure within-test habituation. The data from these trials was not included in the calculation of %PPI.

Block 2, contained 3 types of trials: (1) startle alone pulses, like those in Blocks 1 and 3, (2) no stimulus trials, during which no stimulus other than the background white noise was administered, and (3) prepulse–pulse trials, which consisted of a 20 ms prepulse, either 4, 8, 12, or 16 dB above the background noise, which occurred 100 ms (onset to onset) before the startle pulse. Eight of each of these trial types were administered in pseudorandom order. The %PPI was calculated by the following formula: $PPI = 100 - (P/S) * 100$ where P is the average startle amplitude for prepulse–pulse trials and S is the