Behavioural Brain Research 266 (2014) 85–93

Contents lists available at ScienceDirect

Behavioural Brain Research

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

Research report

Auditory sensory processing deficits in sensory gating and mismatch negativity-like responses in the social isolation rat model of schizophrenia

Louise Witten[a,c,*], Bob Oranje[c,d], Arne Mørk[a], Björn Steiniger-Brach[b], Birte Y. Glenthøj[c], Jesper Frank Bastlund[a]

[a] Synaptic Transmission 1, H. Lundbeck A/S, Otilliavej 7-9, DK-2500 Valby, Denmark
[b] Medical Affairs-Addiction Disorders, H. Lundbeck A/S, Otilliavej 7-9, DK-2500 Valby, Denmark
[c] Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS) and Center for Neuropsychiatric Schizophrenia Research (CNSR), Copenhagen University Hospital, Psychiatric Center Glostrup, Glostrup, Denmark
[d] NICHE, Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX, Utrecht, The Netherlands

HIGHLIGHTS

- We use the rat model of social isolation (SI).
- We test if rats, displays alterations in sensory gating and mismatch negativity (MMN)-like response.
- Alterations in sensory gating are found in SI rats compared with control rats.
- Alterations in MMN-like responses are found in SI rats compared with control rats.

ARTICLE INFO

Article history:
Received 2 December 2013
Received in revised form 20 February 2014
Accepted 24 February 2014
Available online 5 March 2014

Keywords:
Social isolation
Auditory gating
Sensory gating
Mismatch negativity
Schizophrenia

ABSTRACT

Patients with schizophrenia exhibit disturbances in information processing. These disturbances can be investigated with different paradigms of auditory event related potentials (ERP), such as sensory gating in a double click paradigm (P50 suppression) and the mismatch negativity (MMN) component in an auditory oddball paradigm. The aim of the current study was to test if rats subjected to social isolation, which is believed to induce some changes that mimic features of schizophrenia, displays alterations in sensory gating and MMN-like response.

Male Lister-Hooded rats were separated into two groups; one group socially isolated (SI) for 8 weeks and one group housed (GH). Both groups were then tested in a double click sensory gating paradigm and an auditory oddball paradigm (MMN-like) paradigm.

It was observed that the SI animals showed reduced sensory gating of the cortical N1 amplitude. Furthermore, the SI animals showed significant reduction in cortical MMN-like response compared with the GH animals. No deficits in sensory gating or MMN-like response were observed in the hippocampus (CA3) of the SI animals compared with GH animals.

In conclusion, the change in sensory gating of the N1 amplitude supports previous findings in SI rats and the reduced MMN-like response is similar to the deficits of MMN seen in patients with schizophrenia. Since reduced auditory MMN amplitude is believed to be more selectively associated with schizophrenia than other measures of sensory gating deficits, the current study supports the face validity of the SI reared rat model for schizophrenia.

Abbreviations: (MMN), Mismatch negativity; (ERP), Event related potential; (EEG), Electroencephalography; (SI), Socially Isolated; (GH), Group housed; (PND), Postnatal day; (s.c.), Subcutaneous; (ISI), Inter-stimulus interval; (ITI), Inter-trial interval; (CS), Conditioning stimuli; (TS), Test stimuli; (ANOVA), Analysis of variance; (SEM), Standard error of the mean; (MAM), Mitotoxin methylazoxymethanol acetate; (PCP), Phencyclidine; (PPI), Prepulse inhibition.

* Corresponding author at: Synaptic Transmission 1, H. Lundbeck A/S, Otilliavej 7-9, DK-2500 Valby, Denmark.
E-mail addresses: low@lundbeck.com, louise2@cnsr.dk (L. Witten).

http://dx.doi.org/10.1016/j.bbr.2014.02.048
0166-4328/

1. Introduction

Patients with schizophrenia exhibit deficits in various domains that affect their everyday life. Beside the positive and negative symptoms, cognitive impairments are also often associated with the disease and its progression. Unlike psychotic symptoms, cognitive deficits demonstrate an inverse association with social functioning and illness outcome [1,2]. Abnormalities in basic registration, processing, and gating of sensory stimuli, have frequently been observed in patients with schizophrenia [3–5] and might provide an objective index of dysfunctional cognitive processing.

Mismatch negativity (MMN) and sensory gating are two measures that are widely believed to assess different aspects of sensory processing of information. Both processes can be recorded in humans and many animal species (e.g. primates, cats, rabbits, rats and mice) and are thus well suited for conducting translational research.

In humans the P50 event-related potential is a positive deflection seen approximately 50 ms after a response-eliciting stimulus (auditory stimuli in the current study). In a typical P50 suppression paradigm, two identical auditory stimuli are presented to the subject in quick succession (500 ms interstimulus interval). In healthy humans P50 suppression usually occurs: the P50 amplitude to the first (conditioning) stimulus is larger than to the second (testing) stimulus (for review see ref. [6]). The subsequent N100 peak (negative ERP at 100 ms) can also be used to assess a form of gating, which is then referred to as N100 gating [7]. The difference between P50 and N100 gating has not been fully elucidated, but may reflect different underlying neural activity [8–10].

The ERP waveforms obtained in rodents show very similar characteristics as human ERP waveforms with the exception that the latencies of the rodent ERP is approximately 60% shorter [3,11], which has led to the discussion which ERP (e.g. P20 or N40) in the rodent best represents the human P50 (e.g. refs. [11,12]).

In humans the MMN component of the auditory ERP is elicited when infrequent (deviant) sounds occur in a sequence of frequently occurring (standard) sounds; MMN is expressed as the difference between the ERP response to the standard and the deviant tones. It usually peaks between 100 and 240 ms after presentation of the deviant stimulus, depending on the characteristics of the specific paradigm [13].

MMN-like responses have been observed in rats [14–16] and other animal species [17]. Whether MMN-like responses in rodents fully represents human MMN is still under debate [18–20]. Therefore in the current rat study MMN will be referred to as the MMN-like response.

The underlying neurological basis of the generation of MMN activity is not yet fully understood. However, the widely accepted theory is that MMN reflects an automatic orientation reflex which is independent of a subject's attention. As such, MMN is believed to represent neuronal processes that register the difference between a deviant stimulus and the echoic memory trace of preceding standard stimuli [21]. The alternative, more controversially debated [22–25] neuronal adaptation theory argues that MMN could result from the subtraction of a N1 response to a novel sound, from the N1 response to a non-novel (repeated) sound in which the N1 amplitude to the standard sound is depressed due to its decreased novelty [26].

MMN deficits in schizophrenia patients were first described by Shelley et al. [27] and have since then been observed in a number of studies using different paradigm characteristics, i.e. differences in pitch, duration, and intensity of stimuli, as well as inter-stimulus intervals (for summary see ref. [28,29]). Reduced MMN amplitude could reflect impairment in specific brain areas such as the frontal-cortical regions involved in switching involuntary attention [30].

Most of the animal models of schizophrenia require some pharmacological intervention, genetic manipulation or lesions to induce schizophrenia-like symptoms. Studies in rats using the SI rearing model, in which rats are isolated from weaning until adulthood, have shown deficits resembling symptoms and characteristics of schizophrenia pathology. These include impairments in memory and learning [31,32], deficits in PPI [33–35], characteristic changes in the dopamine system on neurochemical [36] and electrophysiological levels [35], disruptions in brain development [37] and behaviour, (e.g. spontaneous hyper-locomotion to novelty [38] or exacerbated behavioural response to amphetamine [35]), increased aggression and deficits in extra dimensional set shifting (for review see [39]). In addition to this construct and face validation, predictive validity of the model has been demonstrated through the effects of antipsychotic treatment [38].

In the present study, sensory gating and MMN were evaluated in SI animals and compared with control animals. We aimed to study the MMN-like response as well as investigating the robustness of the SI model by confirming earlier data on reduced sensory gating in rats reared in isolation [40]. To our knowledge the former has not previously been reported. We hypothesize that in addition to previously demonstrated sensory gating deficits, the SI animals will also display MMN deficits, adding further support to the face validity of the SI reared rat model for schizophrenia.

2. Methods and materials

2.1. Animals

26 male, Lister-Hooded rats (Harlan, The Netherlands) were used for all experiments. These were carried out in accordance with the European Communities Council Directive (86/609/EEC) for the care and use of laboratory animals and the Danish legislation regulating animal experiments. The Danish Animal Experimentation Inspectorate approved the protocols (journal no. 2004/561-798 and 2009/561-1596).

2.2. Isolation procedure

The isolation procedure paradigm applied in the current study has been previously described [37]. Briefly, male rats arrived at the in-house facilities on postnatal days (PND) 8–9 with foster mothers. To reduce the influence of differences in maternal care, all animals were cross-fostered randomly at birth, and litter sizes were standardized to 11 pups each. Upon arrival, dams and pups were left undisturbed until PND 25, when the pups were randomly assigned to one of the two groups: the SI reared rats or the GH rats, raised in groups of five. Housing consisted of a transparent, high, grid-lid macrolon cage, type III or IV, with wood chip bedding (type IV GH; 54 cm × 36 cm × 18 cm; type III IR; 37 cm × 22 cm × 18 cm). No enrichment was provided in either housing group. All animals were housed under controlled temperature (22 ± 1.5 °C) and humidity conditions (55–65%) with a 12-h:12-h light/dark cycle (lights on at 6:00 AM). Handling and noise were kept to a minimum and cages were cleaned twice a week for GH and once a week for SI animals. No further handling procedures were administrated during the first 8 weeks of isolation. Food (Altromin 1324 pills, Brogaarden, DK) and water were freely available. SI and GH animals were kept in the same room facility and could smell, hear, and see each other, but could not get in to physical contact. All testing was conducted after a minimum of 8 weeks of isolation during the light conditions between 9:00 AM and 5:00 PM.