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Aberrant high frequency oscillations recorded in the rat nucleus accumbens in the methylazoxymethanol acetate neurodevelopmental model of schizophrenia

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ABSTRACT

Background: Altered activity of the nucleus accumbens (NAc) is thought to be a core feature of schizophrenia and animal models of the disease. Abnormal high frequency oscillations (HFO) in the rat NAc have been associated with pharmacological models of schizophrenia, in particular the N-methyl-D-aspartate receptor (NMDAR) hypofunction model. Here, we tested the hypothesis that abnormal HFO are also associated with a neurodevelopmental rat model.

Methods: Using prenatal administration of the mitotoxin methylazoxymethanol acetate (MAM) we obtained the offspring MAM rats. Adult MAM and Sham rats were implanted with electrodes, for local field potential recordings, in the NAc.

Results: Spontaneous HFO (spHFO) in MAM rats were characterized by increased power and frequency relative to Sham rats. MK801 dose-dependently increased the power of HFO in both groups. However, the dose-dependent increase in HFO frequency found in Sham rats was occluded in MAM rats. The antipsychotic compound, clozapine reduced the frequency of HFO which was similar in both MAM and Sham rats. Further, HFO were modulated in a similar manner by delta oscillations in both MAM and Sham rats.

Conclusion: Together these findings suggest that increased HFO frequency represents an important feature in certain animal models of schizophrenia. These findings support the hypothesis that altered functioning of the NAc is a core feature in animal models of schizophrenia.

1. Introduction

Over the past 30 years, various neurodevelopmental models have been discovered and refined which are considered to hold more promise for understanding the altered neural circuitry changes taking place during development in schizophrenia (Geyer and Moghaddam, 2002; Lipska and Weinberger, 1993; Marcotte et al., 2001). In recent years the gestational rat methylazoxymethanol acetate (MAM) model has been intensely investigated (Moore et al., 2006). In this model, MAM is administered to pregnant dams at gestation day 17 which leads to disrupted development of limbic-cortical circuits. When the pups reach adulthood they display a variety of histopathological changes in cortical and subcortical regions (although ventricular enlargement is not significant) and develop behavioral changes such as deficits in prepulse and latent inhibition, working memory impairments and potentiated stimulant-induced hyperlocomotion, which validate their use as a model of schizophrenia (Braff and Geyer, 1990; Flagstad et al., 2005; Le et al., 2000, 2006; Talamini et al., 2000). Although animal models are useful for testing possible causative mechanisms, the complex symptoms that underscore a disease like schizophrenia can never be fully modeled in a less cogently developed mammal (Marcotte et al., 2001).

The nucleus accumbens (NAc) integrates information from limbic regions and is involved in cognitive and psychomotor functions (Mogenson et al., 1988). Altered processing of information in limbic networks has been hypothesized to underlie some of the behavioral abnormalities in schizophrenia (Grace, 2000). We have shown previously, that spontaneous high frequency oscillations (130-180 Hz, HFO) can be recorded in local field potential (LFP) of the rodent NAc. HFO in awake rats are enhanced substantially in power following acute injection of N-methyl-D-aspartate receptor (NMDAR) antagonists, and to a lesser extent after administration of serotonergic hallucinogens (Goda et al.,

Abbreviations: NAc, Nucleus accumbens; NMDAR, N - methyl D- aspartate receptor; HFO, High Frequency oscillations; MAM, methylazoxymethanol acetate; spHFO, spontaneous HFO; LFP, Local Field Potential; PSTH, peri stimulus time histogram; E17, embryonic day 17; VTA, ventral tegmental area.

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2013); indicating that altered HFO are associated with pharmacological models of schizophrenia. Although increased HFO power can be recorded in many brain regions in response to NMDAR antagonists (Hiyoshi et al., 2014; Hunt et al., 2011; Kulikova et al., 2012; Nicolas et al., 2011; Phillips et al., 2012b) the NAc appears to be an important locus of this activity (Olszewski et al., 2013a).

In MAM rats, Phillips et al. (2012b) found increased cortical HFO power and reduced gamma power (30-80 Hz) in response to NMDAR antagonists compared to Sham rats. Spontaneous HFO in the hippocampus, also known as ripples does not appear to be altered in the MAM model, since the intrinsic ripple characteristics are not significantly different from controls, although, spike-ripple synchronization is disrupted in MAM rats (Phillips et al., 2012a). Within the NAc, no major spectral differences, up to and including the gamma band, have been reported in MAM rats (Ewing and Grace, 2013). However, it is currently not known whether higher frequencies in the NAc are altered in MAM rats. Given that LFP oscillations in the NAc are fundamentally altered in pharmacological models of schizophrenia (most notably NMDAR antagonism) we tested the hypothesis that HFO would also be altered in the MAM model of schizophrenia. We also examined changes in HFO after administration of the NMDAR antagonist, MK801 and antipsychotic, clozapine.

2. Materials and methods

2.1. Animals

Experiments were performed on the offspring of timed pregnant female Wistar rats, N = 7 that were isolated and received an intraperitoneal (i.p.) injection of 25 mg/kg MAM (methylazoxymethanol acetate, MRIGlobal, USA) or saline at embryonic day 17 (E17) to generate two groups - MAM rats and their controls/Sham rats. They were bred and maintained in the animal house facility at the Nencki Institute. The offspring born to MAM and Sham/saline injected dams were weaned at postnatal day P21 (at par with the standard procedure used for in house animals and in accordance with the protocols of the ethics committee) and as per the description in the previous report (Lodge, 2013). Only the male animals were taken for further experiments. A total of 17 MAM and 17 Sham rats were used in this study. One animal in the MAM group that had misplaced electrodes was excluded from analysis. All animal experiments were carried out according to the European Communities Council Directive of 24 November 1986 (86/609/EEC) and accepted by the local ethics committee. All efforts were made to minimize animal suffering, to reduce the number of animals used and to utilize alternatives to in vivo techniques if available.

2.2. Surgery

Male offspring (280-350 g) were anesthetized with isoflurane and implanted unilaterally with twisted stainless steel electrodes (110 μm, Science Products, Germany), insulated except at the tip and targeted to NAc according to the coordinates of the stereotaxic atlas (Paxinos and Watson, 1998) (AP: +1.6 mm; ML: +1.2 mm; DV:-7.1 mm). A silver wire connected to a skull screw posterior to the bregma was used as the ground/reference. Additional stainless steel hooks and screws were also implanted to hold the socket firmly on the skull. The animals were then transferred to their home cage where they were provided with unlimited access to food and water. 500 mg of paracetamol dissolved in 300 ml of bottled drinking water was provided to the animals for a period of 3-4 days after surgery to ease the surgical pain and facilitate speedy recovery.

2.3. LFP recordings

One week after surgery, the animals were handled for approximately 30 min per day, for 2 days. Following this, LFPs were recorded for 20 min for at least 2 days, to check the signal quality, habituate the animals to the experimental chamber (dimensions: 50 × 44 × 40 cm), and also to the process of connecting/disconnecting to the recording cable. All experiments were performed from 8 AM to 6 PM in a quiet room with dim light and not in darkness. LFPs were recorded using a JFET preamplifier at the head stage, the signals were relayed through a commutator (Crist Instruments, USA), amplified ×1000, filtered 0.1–1000 Hz (A-M Systems, USA), digitized 4 kHz (Micro1401, Cambridge Electronic Design, Cambridge, UK) and stored on a computer for offline analysis.

2.4. Experiments

All animals were recorded for 20 min and then given i.p. injection of either the drug or its vehicle. All experiments were performed according to a Latin square design, whereby every animal received each dose of the drug in a pseudo-randomized order to minimize the number of animals used. The drug washout between consecutive experiments was at least 3 days. For the first set of experiments (N = 8 MAM and N = 11 Sham) after baseline recording for 20 min the animals were given (i.p.) injection of MK801 (0.05, 0.15, 0.3 mg/kg; Sigma Aldrich, Poznan, Poland) or its vehicle (saline) and were recorded for an hour post injection. For experiments using antipsychotics (N = 9 MAM and N = 6 Sham), after 20 min baseline, the animals were first injected (i.p.) with MK801 (0.15 mg/kg) or its vehicle (saline) and then after 30 min they were injected (i.p.) with clozapine (15 mg/kg) or its vehicle – DMSO (Sigma Aldrich, Poznan, Poland) – and recorded for at least an hour. Motor activity of the animal was also measured using beam breaks system; consisting of 15 infrared photocells at a distance of 2.54 cm between each (Columbus Instruments, USA) both during baseline habituation period and also for the duration of the experiments. The device measured the horizontal motor activity and the sum of total activity was analyzed as movement across the chamber.

2.5. Histology

Electrolytic lesions were made and the brains dissected. Electrode placement was identified on 40 μm thick Cresyl violet stained sections. The animals which had the electrodes located in the NAc alone were included for offline analysis.

2.6. Data analysis

Raw LFPs were inspected and large movement artifacts were removed from the signal. From the power spectral analysis using FFT, total power of frequency bands and dominant frequency for HFO typically 130–180 Hz were analyzed in 60 s data bins using FFT of 4096 points (Spike2). The total power of delta (0-4 Hz) and gamma (30-100 Hz) bands were also analyzed. For modulation analysis the accumbal LFPs were digitally filtered (delta: 0.1-4 Hz and HFO: 130–180 Hz). The mean amplitude and standard deviation (SD) of the filtered signals were calculated at baseline for each rat. Events corresponding to a peak, when the trough-to-peak amplitude exceeded 3 and 5 SD, were extracted from the filtered waveforms (Spike2 script) to create event channels. The event channel corresponding to delta 3 SD was used as a trigger channel for peristimulus time histogram (PSTH) of HFO event channel (5 SD) and for calculating the averaged potential of the filtered delta waveform channel. These thresholds were chosen as they correspond to high amplitude delta oscillations and the highest amplitude HFO band. Thus, the threshold values for extracting events were selected on the basis of analysis of amplitudes of delta and HFO bands in baseline and after drugs. PSTHs and averaged potentials were obtained for the last 1000-s period during baseline (BL) and after MK801 injection. The post injection clozapine period was analyzed starting 15 min after injection. Before averaging PSTHs were normalized (i.e. the number of events per bin was divided by the total number of events divided by the number of bins). Normalization was