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Deep brain stimulation of the ventral hippocampus restores deficits in processing of auditory evoked potentials in a rodent developmental disruption model of schizophrenia

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ABSTRACT

Existing antipsychotic drugs are most effective at treating the positive symptoms of schizophrenia but their relative efficacy is low and they are associated with considerable side effects. In this study deep brain stimulation of the ventral hippocampus was performed in a rodent model of schizophrenia (MAM-E17) in an attempt to alleviate one set of neurophysiological alterations observed in this disorder. Bipolar stimulating electrodes were fabricated and implanted, bilaterally, into the ventral hippocampus of rats. High frequency stimulation was delivered bilaterally via a custom-made stimulation device and both spectral analysis (power and coherence) of resting state local field potentials and amplitude of auditory evoked potential components during a standard inhibitory gating paradigm were examined. MAM rats exhibited alterations in specific components of the auditory evoked potential in the infralimbic cortex, the core of the nucleus accumbens, mediodorsal thalamic nucleus, and ventral hippocampus in the left hemisphere only. DBS was effective in reversing these evoked deficits in the infralimbic cortex and the mediodorsal thalamic nucleus of MAM-treated rats to levels similar to those observed in control animals. In contrast stimulation did not alter evoked potentials in control rats. No deficits or stimulation-induced alterations were observed in the prelimbic and orbitofrontal cortices, the shell of the nucleus accumbens or ventral tegmental area. These data indicate a normalization of deficits in generating auditory evoked potentials induced by a developmental disruption by acute high frequency, electrical stimulation of the ventral hippocampus.

1. Introduction

Deep brain stimulation (DBS) is accepted as an alternative therapy for patients refractory to conventional treatments in a variety of movement disorders and is finding increasing application in a large number of other neurological and psychiatric conditions. The most common DBS strategies find application in conditions with histories of successful treatment via surgical ablations leading to the "functional lesion" hypothesis to describe its mechanism of action. Schizophrenia, however, has no such successful history and consequently no immediately obvious stimulation target. As such, despite a desperate need to identify new treatment approaches, the use of DBS as a therapeutic approach in schizophrenia has as yet not been investigated.

Human studies implicate hyperactivity of the anterior hippocampus as a pathological factor in schizophrenia (Malaspina et al., 1999). Reductions in the levels of GAD_{65} and GAD_{67} have been reported in specific subfields of the hippocampus, most notably in layers of CA3/2 and CA1 normally associated with large numbers of GABA neurons (Benes et al., 2007, 2008). This diminished inhibitory control in the hippocampus is thought to contribute to the feed-forward excitation through the hippocampal circuit (Benes et al., 2008) resulting in subicular hyperactivity which may underpin the aberrant regulation of the dopamine system which is central to the manifestation of the positive symptoms associated with the disease (Lodge and Grace, 2007; Grace, 2012). Rodent studies using administration of the mitotoxin methylazoxymethanol acetate (MAM) on gestational day 17 in the rat, a validated animal model of this disorder (Moore et al., 2006; Lodge and Grace, 2009; Hradetzky et al., 2012), also demonstrate ventral hippocampal (the homologous rat brain region) disruption and hyperactivity presumably due to parvalbumin interneuron loss (Penschuck et al., 2006; Lodge et al., 2009). Moreover, the widespread projections of this region to cognitive (medial prefrontal cortex (Hoover and Vertes, 2007)) and affective (amygdala (Canteras and Swanson, 1992)) regions suggest it may impact other symptom classes as well (Grace, 2012). Given the known inhibitory effects of hippocampal stimulation in patients with medial–temporal lobe epilepsy (Boon et al., 2007) it has been hypothesized

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that stimulation of this region may ameliorate the positive symptoms associated with schizophrenia (Mikell et al., 2009).

Among myriad symptom presentations, aberrant auditory processing has long been associated with schizophrenia. Decreased amplitudes in evoked response components with latencies between 50 and 300 ms (Buchsbaum, 1977; Boutros et al., 1993; Ford et al., 1994) and decreased sensory gating (Freedman et al., 1991) are commonly reported. Abnormalities in evoked responses with latencies of approximately 50 ms (P50) have been linked to deficits in gamma band activity in schizophrenia whereas deficits in components with latencies of approximately 100 ms (N100) have been associated with theta activity (Brockhaus-Dumke et al., 2008). It has been suggested that the hippocampus plays a crucial role in the generation of these potentials (Bickford-Wimer et al., 1990; Freedman et al., 1991). Of these disrupted evoked components, it is believed that the longer latency components are due to disruption of attentional processes, whereas the earlier components are more resilient to attentional manipulation (Jerger et al., 1992). Disruption of the earlier components can be replicated in rats by administration of dopaminergic agonists which are reversed by the administration of first generation antipsychotic drugs such as haloperidol (Adler et al., 1986; Bickford-Wimer et al., 1990). These evidences implicate auditory evoked potentials as a valuable proxy measure of the hippocampal disruption and consequent dopamine hyperfunction observed in the MAM-E17 rat model of schizophrenia (Moxon et al., 2003).

In the present study the effects of acute high frequency electrical stimulation of the ventral hippocampus were explored in the MAM-E17 rodent model of schizophrenia. The effects of this stimulation were assessed through examination of auditory evoked potentials and spontaneous local field potentials recorded from multiple regions implicated in the pathophysiology of schizophrenia-like symptoms in the rat, including: the prelimbic-, infralimbic- and orbitofrontal-cortices, the ventral striatum, the mediodorsal thalamic nucleus, the ventral tegmental area and the ventral hippocampus.

2. Materials and methods

2.1. Animals and surgery

All experiments were performed in accordance with the United States Public Health Service "Guide for the Care and Use of Laboratory Animals" and were approved by the Institutional Animal Care and Use Committee of the University of Pittsburgh.

Timed pregnant female Sprague–Dawley rats were obtained at gestational day 15 and housed individually with free access to food and water. A DNA methylating agent (methylazoxymethanol (MAM) in saline) or vehicle (saline) was administered (20 mg/kg, 1 ml/kg, i.p.) on gestational day 17. Male pups were weaned on post-natal day 21 and housed in groups of two or three with free access to food and water. Experiments occurred no earlier than 12 weeks of age.

Rats weighing 560–610 g (mean = 583 g, n (MAM) = 10, n (SAL) = 8, 18 total) were anesthetized with isoflurane (induction: 5%, maintenance: 2% in oxygen) and mounted in a stereotaxic frame. Carprofen (Rimaydyl™) was administered for analgesia (5 mg/kg s.c.). Body temperature was maintained with a small heating pad (Fintronics Inc.). The scalp was incised, the skull exposed and burr holes drilled. LFP electrodes were implanted bilaterally into the prelimbic (RC[1]: +3.4, ML: ±0.7 mm, DV: −4.0 mm), infralimbic (RC: +3.4, ML: ±0.7 mm, DV: −5.0 mm) and orbitofrontal cortices (RC: +3.2, ML: ±3.4 mm, DV: −5.0 mm, PrL, IL and OFC respectively), the core (RC: +1.2, ML: ±2.0 mm, DV: −7.2 mm) and shell (RC: +1.2, ML: ±2.0 mm, DV: −8.0 mm) of the nucleus accumbens (AcbC, AcbSh respectively), the mediodorsal thalamic nucleus (RC: −3.3, ML: ±0.7 mm, DV: −5.5 mm, MD) and the ventral tegmental area (RC: −5.3, ML: ±0.7 mm, DV: −8.5 mm, VTA). Custom made dual recording/stimulating electrodes were implanted, bilaterally, into the ventral hippocampus (RC: −6.0, ML: ±4.5 mm, DV: −8.2 mm, vHipp). Two ground screws were affixed either sides of lambda and 6 additional stainless steel screws fixed in the skull. All electrodes and connectors (E363, Plastics 1) were secured with dental cement and the incision sutured tightly around the implant. Animals were housed singly following surgery, given free access to rat chow softened with children's Tylenol for the first 2 days and allowed to recover for at least a week before beginning recordings.

2.2. Data acquisition

Local field potential (LFP) recording electrodes (125 μm, polyimide insulated, stainless steel wire) and stainless steel screw electrodes were obtained from Plastics 1. Custom-made dual recording/stimulating bipolar-concentric electrodes were fabricated by feeding 125 μm, polyimide insulated, stainless steel wire through 26 G stainless steel tubing. A third 125 μm LFP recording electrode was affixed to the outside of the tubing to allow simultaneous stimulation and recording from the same site. The stainless steel tubing was insulated with miniature heatshrink tubing (Plastics 1).

Animals were tethered to the recording system (RHA2000-EVAL board, Intan Technologies, LLC) via a custom-made 11 channel cable and commutator (Plastics 1). All recordings were made against the ground screws affixed above the cerebellum. LFPs were amplified (gain = 800), high pass filtered at 1 Hz, low pass filtered at 7.5 kHz and sampled at 25 kHz. Animals were habituated to the recording apparatus over 3 days before beginning data acquisition. Auditory evoked potential event markers were recorded via one of the auxiliary inputs on the RHA2000-EVAL board. Recordings were made while animals were loosely restrained within a 4 l glass jar. The jar was placed inside a sound attenuated chamber (SR lab, San Diego Instruments) and auditory stimuli presented via a speaker mounted in the roof of the chamber. Testing for each animal consisted of the presentation of 100 identical pairs of white noise auditory stimuli (15 dB above background (60 dB), 10 ms duration, 500 ms interstimulus interval, 10 s intertrial interval) (Mears et al., 2009).

2.3. Stimulation

Custom designed stimulation devices were fabricated for the continuous delivery of chronic DBS in the rat. Devices were configured to stimulate with square, monophasic constant current 100 μs pulses at a frequency of 130 Hz delivered at an amplitude of 200 μA. Stimulation began at the start of the testing session (5 min before the first stimulus presentation) and was delivered continuously throughout (approximately 20 min). Animals were randomly allocated by stimulation protocol (stimulation or sham) and time of day. They performed the inhibitory gating tests twice on consecutive days based on the double test cross-over design which is purported to have greater sensitivity (Leyland et al., 1979). Animals would either be receiving stimulation or sham-stimulation (attachment of devices and connectors but no delivery of current) in each of the two sessions in a counterbalanced design with half of the animals receiving stimulation on the first day of testing and sham-stimulation on the following day with these conditions reversed in the remaining animals.

2.4. Signal processing

Auditory evoked potentials were identified (via the event marker) and extracted for 0.3 s preceding and 0.5 s following the stimulus presentation. These signals were then processed to remove electrical artifacts caused by stimulation using custom written algorithms based on those developed by others (Erez et al., 2010). Briefly, the evoked

[1] Abbrev.: RC, rostrocaudal; ML, mediolateral; and DV, dorsoventral.