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Research Paper

Deep brain stimulation improves behavior and modulates neural circuits in a rodent model of schizophrenia

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ABSTRACT

Schizophrenia is a debilitating psychiatric disorder with a significant number of patients not adequately responding to treatment. Deep brain stimulation (DBS) is a surgical technique currently investigated for medically-refractory psychiatric disorders. Here, we use the poly I:C rat model of schizophrenia to study the effects of medial prefrontal cortex (mPFC) and nucleus accumbens (Nacc) DBS on two behavioral schizophrenia-like deficits, i.e. sensorimotor gating, as reflected by disrupted prepulse inhibition (PPI), and attentional selectivity, as reflected by disrupted latent inhibition (LI). In addition, the neurocircuitry influenced by DBS was studied using FDG PET. We found that mPFC- and Nacc-DBS alleviated PPI and LI abnormalities in poly I:C offspring, whereas Nacc- but not mPFC-DBS disrupted PPI and LI in saline offspring. In saline offspring, mPFC-DBS increased metabolism in the parietal cortex, striatum, ventral hippocampus and Nacc, while reducing it in the brainstem, cerebellum, hypothalamus and periaqueductal gray. Nacc-DBS, on the other hand, increased activity in the ventral hippocampus and olfactory bulb and reduced it in the septal area, brainstem, periaqueductal gray and hypothalamus. In poly I:C offspring changes in metabolism following mPFC-DBS were similar to those recorded in saline offspring, except for a reduced activity in the brainstem and hypothalamus. In contrast, Nacc-DBS did not induce any statistical changes in brain metabolism in poly I:C offspring. Our study shows that mPFC- or Nacc-DBS delivered to the adult progeny of poly I:C treated dams improves deficits in PPI and LI. Despite common behavioral responses, stimulation in the two targets induced different metabolic effects.

1. Introduction

Schizophrenia is a debilitating psychiatric disorder with a lifetime prevalence of approximately 1% (Tamminga and Holcomb, 2005). Despite the development of new medications, about 30% of patients do not adequately respond to pharmacological treatment (Falkai et al., 2005, 2006). Deep brain stimulation (DBS) is a surgical technique that involves the delivery of electrical current to the brain parenchyma through implanted electrodes. In psychiatry, DBS has been approved for treatment-resistant obsessive-compulsive disorders (Hamani et al., 2014b) and is currently being investigated for depression (Holtzheimer et al., 2012; Lozano et al., 2008; Malone et al., 2009; Mayberg et al., 2005), anorexia (Lipsman et al., 2013), Alzheimer's disease (Kuhn et al., 2015; Laxton et al., 2010) and drug addiction (Muller et al., 2013; Stelten et al., 2008; Voges et al., 2013). So far, though different targets have been proposed (Ewing and Winter, 2013; Mikell et al., 2009), no clinical trials have been reported on the use of DBS in schizophrenia.

Schizophrenia is a complex and multi-symptomatic disorder. The well-documented association between intrauterine inflammatory/immunologic responses (e.g. to infectious agents) and the susceptibility for the development of schizophrenia promoted the establishment of the so-called "maternal immune activation" (MIA) models (Baharnoori et al., 2012; Piontkewitz et al., 2012a). These involve

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administering pregnant dams with viruses, bacterial products (i.e. lipopolysaccharides) or viral mimics, such as polyinosinic-polycytidilic acid (poly I:C) (Meyer, 2014). The progeny born after such insults develop neuropathological and behavioral changes that somewhat mimic those observed in schizophrenia. Some of these include deficits in sensorimotor gating, as reflected by a decrease in prepulse inhibition (PPI), attentional selectivity deficits, as reflected in disrupted latent inhibition (LI), decreased hippocampal and prefrontal cortex and increased ventricular volumes, and reduced hippocampal neurogenesis (Ozawa et al., 2006; Piontkewitz et al., 2011, 2012a; Piontkewitz et al., 2009; Piontkewitz et al., 2012b). Notably, the full spectrum of behavioral abnormalities only emerges after the offspring have reached late adolescence or early adulthood (Hadar et al., 2015; Piontkewitz et al., 2011; Zuckerman et al., 2003), which is consistent with the post-pubertal emergence of full-blown phenotype in schizophrenia (Tandon et al., 2009).

In a previous report, we have shown that DBS at high frequencies applied to the medial prefrontal cortex (mPFC) and dorsomedial thalamus of the adult offspring of poly I:C injected dams normalized PPI deficits (Klein et al., 2013). In this study, we extend that line of research by investigating the behavioral effects of mPFC and nucleus accumbens (Nacc) DBS applied to adult rats on both the PPI and LI paradigms. Based on the fact that DBS is known to influence structures at a distance from the stimulated target (Hamani and Temel, 2012) and given the strong anatomical and functional links between mPFC and Nacc (Hamani et al., 2011; Vertes, 2004) we hypothesize that both mPFC and Nacc stimulation will affect the characteristic behavioral deficits of poly I:C offspring in both PPI and LI by specifically modulating neurocircuits involved in schizophrenia. To study the neurocircuitry influenced by DBS we have used glucose uptake positron emission tomography (PET) imaging (Klein et al., 2011).

2. Materials and methods

2.1. Animals

Rats were housed 2–4/cage in a temperature and humidity controlled vivarium with a 12-h light–dark cycle and with food and water ad-libitum. Experiments were performed during day time (lights on for PPI and PDG-PET studies, and lights off for LI studies), according to the guidelines of the European Union Council Directive 2010/63/EU for care of laboratory animals and were approved by the local ethic committee (Senate of Berlin, Germany for PPI experiments, Animal Care and use Committee, Tel Aviv University, Israel for LI experiments and Ethics Committee for Animal Experimentation of Hospital Gregorio Marañón Madrid, Spain for FDG-PET studies and the Centre for Addiction and Mental Health).

2.2. Experimental design

Wistar rats (Harlan Laboratories, Germany, Israel and Spain) were mated and the first day after copulation was defined as day 1 of pregnancy. On gestation day 15, pregnant dams were given a single i.v. injection to the tail vein of either poly I:C (4 mg/kg; SIGMA, Germany) dissolved in saline, or saline alone under light isoflurane anesthesia (Hadar et al., 2015). On post-natal day (PND) 21, pups were weaned and housed according to sex and litter. Experimental groups consisted of male offspring derived from multiple independent litters. Surgery was performed on adult offspring (PND > 90), bilateral electrodes were implanted into either the mPFC or the Nacc shell. Behavioral and imaging experiments commenced 1–2 weeks *post-surgery*. During the last 5 days of recovery, rats were handled for about 10 min daily. Handling comprised habituation to the investigator, the stimulation procedure, i.e. connection of the electrodes to the cable system, and if applicable, the testing chamber. DBS was conducted during PPI testing for 40 min, during pre-exposure and conditioning stages of the LI paradigm for 30 and 15 min and during FDG uptake periods for 45 min at 130 Hz, 150 μA and a pulse duration of 90 μsec (biphasic stimulation mode). These parameters were chosen as they were found to be the most effective in our previous experiments with this model (Klein et al., 2013). DBS was performed with an isolated stimulator (MultichannelSystems; Coulbourn Instruments, Allentown, PA, USA) connected to the electrodes via an isolated cable system hanging from the ceiling of the behavioral apparatus and a swivel.

2.3. Surgery

Surgery was conducted under general anesthesia (PPI experiments: fentanyl (0.005 mg/kg i.m., Janssen-Cilag, Germany), midazolam (2 mg/kg i.m., Hameln, Germany), medetomidine dihydrochloride (0.135 mg/kg i.m., Elanci Animal Health, Germany), antagonized upon completion with naloxone (0.12 mg/kg i.m. Inresa Arzneimittel, Germany), flumazenil (0.2 mg/kg i.m, HEXAL Germany) and atipamezolhydrochlorid (0.75 mg/kg s.c. Elanco Animal Health, Germany); LI experiments: isoflurane (Nicholas Piramal, Northumberland, United Kingdom) followed by avertin (20 ml/kg i.p.); imaging: ketamine (100 mg/kg i.p., Pfizer, Ortaköy-Istanbul, Turkey) and xylazine 1 mg/kg i.p., Calier, Barcelona, Spain). Cathodes (monopolar platinum–irridium electrodes with connector; Plastics One, Roanoke, USA) were bilaterally implanted into the mPFC (more specifically into the ventral prelimbic cortex; anteroposterior (AP) +3.5, mediolateral (ML) 0.6, dorsoventral (DV) −3.4) or the Nacc shell (AP +1.2, ML 1.5, DV −8.2), as previously described (Klein et al., 2013). Anodes were wrapped around anchor screws implanted in close proximity to the stimulating electrode. Electrode placement was confirmed in cresyl violet stained sections or imaging. For the former, rats were anaesthetized and transcardially perfused with 0.9% saline followed by 4% paraformaldehyde (PFA). For the latter, computed tomography (CT) scans were obtained and co-registered to a reference MRI study (anatomical MRI template obtained from a non-operated animal). Only animals with correct electrode placement were included in the study (Fig. 1a + b).

2.4. Behavior

2.4.1. Prepulse inhibition (PPI)

PPI of the acoustic startle reflex (ASR) was measured in three sessions given 24 h apart. Session 1 (baseline 1) was conducted without stimulation. Session 2 was conducted while animals received either mPFC or Nacc-DBS. Session 3 (baseline 2) was carried out with no DBS applied to assess whether the observed effects in Session 2 were permanent or transient, i.e. effect not noticed 24 h after DBS. During test sessions, animals were placed in a wire mesh cage mounted on a transducer-platform. Loudspeakers on both sides of the cage were used for acoustic stimulation. Sessions began with a 5 min acclimatization phase, which was followed by the PPI test. During acclimatization, animals were exposed to background noise followed by 10 startle stimuli (20 ms each). The test session consisted of 7 different types of trials administered in a pseudorandom order: 1) pulse alone (100 dB sound pressure levels (SPL) white noise, 20 ms duration); 2) control (no stimulus); 3–4) prepulse alone (72 dB or 68 dB, pure tone, 10 Hz, 20 ms duration); 5–7) prepulse (72 dB, 68 dB, or 64 dB) followed by pulse (100 ms interstimulus interval). Animals received a total of 10 presentations of each type. Background noise intensity during the whole experiment was 60 dB SPL. PPI was calculated according to the formula 100–100% × (PPx/PA), in which PPx is the ASR of the 10 PPI trials for each individual prepulse intensity and PA is the mean ASR of the pulse alone trials. The average PPI response over the three pre-pulse intensities was analyzed (Klein et al., 2013; Mattei et al., 2014).

2.4.2. Latent inhibition (LI)

LI was measured in a thirst-motivated conditioned emotional response (CER) procedure by comparing the suppression of drinking to a tone previously paired with a foot-shock in rats that received non-reinforced exposure to the tone before conditioning (pre-exposed, PE)