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What rodent models of deep brain stimulation can teach us about the neural circuit regulation of prepulse inhibition in neuropsychiatric disorders

Kerstin Schwabe *, Joachim K. Krauss

Department of Neurosurgery, Medical University Hannover, Carl-Neuberg-Str. 1, D-30625 Hannover, Germany

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ABSTRACT

Deep brain stimulation (DBS) is routinely used for treatment of movement disorders and it is also under investigation for neuropsychiatric disorders with deficient sensorimotor gating, such as schizophrenia, Tourette's syndrome and obsessive compulsive disorder. Electrical stimulation induces excitation and inhibition both at the stimulation site and at projection sites, thus modulating synchrony and oscillatory behavior of neuronal networks. We first provide background information on DBS in neuropsychiatric disorders accompanied by deficient sensorimotor gating. We then introduce prepulse inhibition (PPI) as a measure for sensorimotor gating in these disorders. Thereafter, we report on the use of DBS in rat models with deficient PPI induced by pharmacologic, genetic and neurodevelopmental manipulation. These models offer the opportunity to define the neuronal circuit regulation that is of relevance to PPI and its deficits in neuropsychiatric disorders with disturbed sensorimotor gating. Finally, we report on the use of the PPI paradigm in human patients operated for DBS *on*/*off* stimulation, which may further elucidate the neuronal network involved in regulation of PPI.

1. Introduction

Disturbed sensorimotor gating has been described in various neuropsychiatric disorders, including schizophrenia, Tourette's syndrome (TS) and obsessive compulsive disorder (OCD; Kohl et al., 2013; Swerdlow et al., 2008). It has been linked conceptually to the inability to filter or "gate" irrelevant or interfering information in motor, cognitive and emotional domains, with subsequent sensory overload and clinical symptoms. Pathophysiologically, a dysregulation of neuronal network activity between cortex and associative-limbic basal ganglia-thalamic loops is discussed (DeLong and Wichmann, 2007; Kopell and Greenberg, 2008; Swerdlow and Koob, 1987). In cases of pharmacoresistant TS and OCD high frequency deep brain stimulation (DBS) is used for modulation of neuronal network activity and relief of symptoms (Krack et al., 2010). In schizophrenia DBS is controversially discussed as a possible therapeutic option (Mikell et al., 2016, 2009).

Electrophysiological recordings of patients undergoing DBS procedures are possible during, or shortly after implantation of the DBS electrodes. This approach, however, has limitations since the recording site depends on clinical needs and is only partially driven by theoretical considerations. With that regard, the use of experimental animals allows probing the neuronal network activity at relevant key sites in relation to functional and behavioral dysfunction. One approach to assess sensorimotor gating processes in a cross species manner is prepulse inhibition (PPI) of the acoustic startle response. In patients with the aforementioned neuropsychiatric disorders (schizophrenia, TS and OCD) deficient PPI has been described as a common factor (Kohl et al., 2013; Swerdlow, 2013; Turetsky et al., 2006). Experimentally-induced reduction of PPI in rodents therefore has been regarded an endophenotype for deficient sensorimotor gating and thought to be useful to investigate the underlying pathophysiological mechanisms (Swerdlow et al., 2001).

In this review we first introduce the method of DBS and its use in neuropsychiatric disorders accompanied by deficient sensorimotor gating. Thereafter, we will give an overview on the PPI paradigm in this context. Finally, we will report on the use of DBS in animal models with pharmacologically, genetically and neurodevelopmentally induced deficient PPI, which offers the opportunity to define the neuronal circuit regulation that is of relevance to PPI and its deficits in certain neuropsychiatric disorders. The use of the PPI paradigm in human patients operated for DBS may further elucidate the network involved in regulation of PPI.

2. Deep brain stimulation

Deep brain stimulation is well established for treatment of movement disorders, especially Parkinson disease, tremor and dystonia, and

* Corresponding author.
E-mail addresses: schwabe.kerstin@mh-hannover.de (K. Schwabe), krauss.joachim@mh-hannover.de (J.K. Krauss).

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in certain pain syndromes, with more than 150,000 patients operated so far (Boccard et al., 2015; Fasano et al., 2015). In neuropsychiatric disorders, however, this treatment is still under investigation or in the early stages. For DBS, electrical current is chronically delivered through stereotactically implanted electrodes into specific brain regions via a subcutaneously implanted pacemaker. Typically, square biphasic waveforms with a frequency of 130 Hz, a pulse width of 60 to 210 μs and amplitude of 2–5 V are used.

The pathophysiological mechanisms of DBS are not fully understood. Initially DBS was described as a "functional" lesion, but it is now recognized that DBS acts by complex modulation of neuronal networks, such as excitation and inhibition at the stimulation site as well as in projection sites, leading to altered network synchrony and oscillatory behavior (DeLong and Wichmann, 2012). Furthermore, the clinical effects of DBS can occur both acutely and in a delayed and progressive fashion. Most likely, delayed effects are the result of plasticity changes in the network, whereas the short-term improvements result from the immediate effects of DBS. Another hypothesis about the effect of DBS is overwriting of pathological activity by introducing a frequency that interferes with the pathological message (Krack, 2011).

DBS is not only a therapeutic technique. The insertion of stimulation electrodes and the application of electrical stimulation within dysfunctional neuronal circuits present the unique opportunity to study the pathophysiological characteristics of certain disorders, but also the dynamics of neuronal circuitries in relation to normal brain function. Microelectrode recordings along brain trajectories in conscious humans allow identification of the electrophysiological signatures of different brain sites. Further, the ability to externalize the electrodes allows recording of neuronal oscillatory activity within the brain while the patient performs cognitive, emotional or motor tasks. Stimulation can also be coupled to functional neuroimaging studies (Lozano and Lipsman, 2013).

Human stereotaxy was initially used to treat psychiatric diseases with circumscribed lesions or focal electrical stimulation in certain subcortical brain structures. In the early 1950s, Robert Heath, a psychiatrist from Tulane University, New Orleans, started a program of early DBS in several subcortical nuclei and pathways for treatment of schizophrenia, as well as pain and epilepsy. Benefits of stimulation in patients with schizophrenia, however, were limited. Later, Heath lost his reputation when using septal self-stimulation, which some patients described as "pleasant" or "euphoric", for dubious reasons. Such abuses of early attempts with stimulation techniques together with the indiscriminate use of leucotomy in the lobotomy era, led to the demise of psychosurgery altogether (reviewed in: Hariz et al., 2010; Krack et al., 2010).

Modern DBS in thalamic regions was introduced in the late 1980s as an alternative for the treatment of tremor (Benabid et al., 1993). Before, it had been used for treatment of neuropathic pain and in rare instances of movement disorders (Mundinger, 1977; Mundinger and Neumüller, 1982). After thalamic DBS became accepted as a treatment for tremor, it was also applied for stimulation of the pallidum in PD (Siegfried and Lippitz, 1994). Findings of excessive burst activity in the subthalamic nucleus (STN) in the MPTP treated nonhuman primate Parkinson model (Miller and DeLong, 1987), together with improvement of parkinsonian features after STN lesions or stimulation (Aziz et al., 1991; Benazzouz et al., 1993; Bergman et al., 1990), led to the successful application of STN DBS in a patient with advanced PD (Pollak et al., 1993). Over the next few years, STN DBS gained wide popularity, largely replacing pallidotomy for PD (Starr et al., 1998). The next step forward was the introduction of pallidal DBS for the treatment of dystonia (Coubes et al., 2000; Krauss et al., 1999).

In the field of psychiatry DBS was re-introduced in TS and OCD to modulate neuronal activity in areas that were successfully lesioned before. In 1999, Vandewalle used the border between the thalamic ventral oralis internus (Voi)/centromedian-parafascicular nucleus (CM-Pf) for DBS in TS, i.e., areas that had been previously stereotactically lesioned by Hassler and Dieckmann (Vandewalle et al., 1999). Although in the majority of the cases the Voi/CM-Pf was used thereafter, numerous other targets have also been tried for DBS in TS (reviewed in Akbarian-Tefaghi et al., 2016; Hariz and Robertson, 2010; Testini et al., 2016; Viswanathan et al., 2012), including the globus pallidus internus (GPi). Both, the sensorimotor region and the associative-limbic region of the GPi have been targeted to alleviate tics in TS by DBS (Cavanna et al., 2011; Kefalopoulou et al., 2015; Martínez-Fernández et al., 2011; Sachdev et al., 2014). The ventral striatum and the nucleus accumbens (NAC) have been targeted as well (Houeto et al., 2007; Müller-Vahl, 2013; Porta et al., 2012; Shahed et al., 2007) to treat comorbid obsessive compulsive symptoms in TS (Ackermans et al., 2013, 2011; Hariz and Robertson, 2010; Porta et al., 2012; Shahed et al., 2007).

Nuttin introduced DBS of the anterior limb of the internal capsule for OCD in 1999, which had been targeted earlier for lesioning by Leksell (Nuttin et al., 1999). While the NAC had been favored as a target several years ago (van Kuyck et al., 2007), some groups now moved the target posterior to the anterior commissure aiming at the bed nucleus of the stria terminalis (Luyten et al., 2016). In addition, the STN and the inferior thalamic peduncle have been used (Kohl et al., 2014). Two trials on NAC stimulation for OCD used a double blind crossover phase with 10 patients (Huff et al., 2010) and 16 patients (Denys et al., 2010), respectively, and reported beneficial outcome. Remarkably, DBS for OCD is the only application with FDA approval in a neuropsychiatric disorder.

Despite the precarious history of neurosurgery in this disorder, more recently different reviews asked the question whether the technical and pathophysiological knowledge would be sufficient to try DBS as a treatment option in schizophrenia (Mikell et al., 2016, 2009). However, in contrast to TS and OCD, no valid expertise regarding putative anatomical targets in schizophrenia can be drawn from previous neurosurgical approaches. A recent meta-analysis demonstrated that of more than 170 individuals who had been treated with ablative procedures (mainly cingulotomy and callosotomy), patients diagnosed with addiction and schizophrenia showed the least improvement from surgery (Leiphart and Valone, 2010). With regard to the dopamine dysregulation hypothesis in schizophrenia, several authors suggested the NAC or ventral striatum as a possible target. Other targets, which have been proposed for DBS include the mediodorsal thalamus, the internal globus pallidus (GPi), and the subcallosal cingulate gyrus (CG25; Mikell et al., 2016, 2009; Salgado-López et al., 2016).

Schizophrenia, however, is a syndromatic disorder, i.e., a collection of various symptoms with largely unknown pathophysiology, certainly not caused by a single brain damage or a localized brain deficit. Although in different psychiatric applications DBS of the NAC (OCD) or the subgenual cingulum (depression) have been proven to be safe (review by Kuhn et al., 2011), applying DBS in schizophrenia remains controversial, and would require extreme caution and adherence to high ethical standards (Nuttin et al., 2014). So far, two clinical trials have been registered for DBS in treatment-resistant schizophrenia: one ongoing prospective randomized, double-blind clinical trial in Toronto that targets the VS (clinicaltrials.gov no. NCT01725334; 16), and one trial in Spain that employs placements in either the NAC or the subgenual anterior cingulate cortex (clinicaltrials.gov NCT02377505). Thus far, one report has been published showing improvement of both positive and negative symptoms in a patient with schizophrenia treated with NAC DBS (Corripio et al., 2016). The authors of this study since then have reported about the safety and feasibility of DBS in 5 patients with schizophrenia in abstract form (Salgado et al., 2017).

Together, DBS for any psychiatric or behavioral disorder still remains at an investigational stage. The identification of the networks, including their key elements, their dynamic properties and their disturbances in certain disorders are still incompletely understood.

3. Prepulse inhibition as a measure for deficient sensorimotor gating in neuropsychiatric disorders

The ability to suppress or gate irrelevant information in sensory, cognitive and motor domains is important to hierarchically order relevant

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