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Review

Deep brain stimulation in Huntington's disease: Assessment of potential targets

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ABSTRACT

Huntington's disease (HD) is an autosomal-dominant neurodegenerative disorder that has very few effective therapeutic interventions. Since the disease has a defined neural circuitry abnormality, neuromodulation could be an option. Case reports, original research, and animal model studies were selected from the databases of Medline and PubMed. All related studies published up to July 2014 were included in this review. The following search terms were used: "Deep brain stimulation," "DBS," "thalamotomy," "pallidal stimulation," and "Huntington's Disease," "HD," "chorea," or "hyperkinetic movement disorders." This review examines potential nodes in the HD circuitry that could be modulated using deep brain stimulation (DBS) therapy. With rapid evolution of imaging and ability to reach difficult targets in the brain with refined DBS technology, some phenotypes of HD could potentially be treated with DBS in the near future. Further clinical studies are warranted to validate the efficacy of neuromodulation and to determine the most optimal target for HD.

1. Introduction

Huntington's disease (HD) is an autosomal-dominant neurodegenerative disorder that is progressive in nature and universally fatal. Huntingtin, the mutant gene at the root of the disease, is the result of an expanded CAG repeat on the short arm of chromosome 4. It is normal to have CAG repeats in the human genome, but when these repeats reach 41 or more, the disease manifests and becomes fully penetrant [1]. This CAG repeat leads to a polyglutamate strand at the N-terminus and confers a gain of function that is toxic in nature. HD results in impairments of motor function, cognitive decline, and psychiatric impairment [2]. The onset of these symptoms is generally in middle-age, but the disorder can become symptomatic at any time of life [3].

Chorea is the hallmark movement-related symptom of this disease and is generally present at the time of diagnosis, except for rare manifestation of bradykinesia or catatonia (Westphal variant or juvenile HD) [4]. While the presence of chorea is helpful in the actual diagnosis of the disorder, it is not useful as a marker of disease severity. Chorea tends to progress, but then becomes less prominent as later symptoms of dystonia and rigidity become apparent [5]. However, motor impersistence (defined as the inability to maintain voluntary muscle contraction) is another common finding and appears to be linearly progressive in nature. The linear progressiveness of this may show it as being more useful physical marker for monitoring disease severity as compared to chorea [2]. Affected individuals also show incoordination, difficulty with fine motor skills, and slowed saccadic eye movements [6].

When the movement related symptoms of the disease become disabling, patients are generally started on pharmacologic treatment to improve their quality of life. These medications generally include tetrabenazine or neuroleptics (both typical and atypical) that result in decreased action of dopamine, with the goal of decreasing the hyperkinetic disorder. Titration of these medications becomes difficult as these medications can commonly cause bradykinesia, rigidity, depression, and sedation [7]. The lack of efficacy of many HD medications and the adverse effects of current medications has led to an interest in determining one or possibly multiple, optimized targets for deep brain stimulation (DBS) in the treatment of HD, reflecting the pathophysiology of HD as a circuit disorder. In this review, we attempt to elucidate the pathophysiology, pertinent animal studies and the current neuromodulation options for HD.

2. Pathophysiology of HD

The basic pathophysiology of neurodegenerative conditions including HD is not completely understood. Recently, the zebrafish model has been explored to elucidate the pathophysiological mechanism underlying HD [8]. Classically, cortico–striato–pallido–thalamo–cortical circuits have been implicated in the pathophysiology of a variety of movement disorders including Parkinson's

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disease (PD) and HD [9]. The striatum serves as the input nucleus into the basal ganglia–thalamocortical circuitry and projects neurons to either the globus pallidus externus (GPe; indirect pathway) or globus pallidus internus (GPi; direct pathway) [9,10]. When the direct pathway is stimulated it leads to disinhibition of the thalamus, thus increasing thalamocortical activity and facilitating movement. The opposite is true of the indirect pathway and leads to increased inhibition of the thalamus and decreased thalamocortical activity, therefore inhibiting movement. Using optogenetic techniques, activation of direct pathway has been shown to correlate with inhibited substantia nigra pars reticulata (SNr) neurons, whereas activation of indirect pathway correlated with excited SNr neurons [11]. Therefore the basal ganglia output nuclei can be modulated by the striatal inputs via the direct or indirect pathways leading to activation or inhibition of thalamocortical circuits, respectively. Recently, co-activation of direct and indirect pathways has been implicated in the initiation of appropriate contraversive motor tasks and inhibition of opposite motor tasks [12,13].

HD selectively leads to cell loss and atrophy of the caudate and putamen, and it appears that striatal medium spiny neurons are the most vulnerable. Furthermore, the cells that contain enkephalin and project to the GPe are more affected than the cells containing substance P that project to the GPi [1,2]. Due to the GPe being more affected, there is a preferential involvement of the indirect pathway of the basal ganglia–thalamocortical circuitry. This reduced inhibition of the GPe leads to excessive inhibition of the subthalamic nucleus (STN) and hyperstimulation of the motor cortex downstream [10]. Chorea is the end result of this hyperstimulation. The preferential involvement of the fibers projecting to the GPe can also explain the findings of bradykinesia and dystonia that are seen in HD patients later in the disease course. When there is increased activity in the GPe, there will be increased inhibition of the GPi. Microelectrode recordings have been compared in patients with HD to those in PD and it was found that the GPi neuronal discharge was significantly lower in the HD patients as compared to the PD patients [14]. As the disease progresses there is also nonselective involvement of the striatal cells that involve both the direct and indirect pathways.

3. Why neuromodulation is a possibility in HD

Indications of DBS have evolved over last two decades and have been investigated in many other disorders (including depression, Tourette's syndrome, epilepsy, post-stroke pain, amputation pain, trigeminal neuralgia, addiction and eating disorders, traumatic brain injury, post-traumatic stress disorders, impaired conscious state and dementias) apart from PD and tremors with varied success [15–23]. Basic or ideal pre-requisites for neuromodulation for any neurological disorders may include to following.

- The disease should have a defined phenotype.
- The disease should have an established and understood neural network.
- There should be evidence that nodes in the network modulate output.
- Surgical access to those nodal points (targets) should be technically feasible.
- There should be defined assessment scales.
- There should be adequate animal experiment data.
- There should safety and efficacy human patient data.

The present literature, though sparse, seems to fulfill most or a part of these pre-requisites except the neural networks involved in the pathophysiology of HD, which are yet to be completely understood.

4. Literature search

The English language literature was searched for various studies including case reports, original research, and animal model studies from the databases of Medline and PubMed describing the DBS in patients with Huntington's chorea. All related studies published up to July 2014 were included in this review. The following search terms were used: "Deep brain stimulation," "DBS," "thalamotomy," "pallidal stimulation," and "Huntington's Disease," "HD," "chorea," or "hyperkinetic movement disorders."

5. Current targets

5.1. GPi

At the time of writing, few cases of DBS used to treat HD have been reported in the literature (Table 1). The majority of the cases have used the GPi as the target of choice due to its known effectiveness at reducing levodopa induced dyskinesia in PD patients [24,25] and it being the target of choice for any hyperkinetic disorder. The goal of DBS with the GPi as the target is reduction in the choreiform movements that are often disabling to these patients. In addition, dystonia in HD can be troublesome and is difficult to treat with medications. All anti-dystonia medications will worsen the psychiatric symptoms. So the GPi could be a target of choice in early onset HD, which is usually accompanied by a predominant dystonic component.

Moro et al. conducted the first study in bilateral GPi DBS in a 43-year-old man and found a clinical reduction in chorea and dystonia at low frequency (40 Hz) stimulation without increase in bradykinesia [25]. Increasing stimulation lead to further reduction in chorea, but also lead to worsening of bradykinesia. This preference for lower frequency stimulation was also found in a similar study conducted by Fasano et al. [24] which showed the same worsening of bradykinesia as stimulation was increased, but with similar decrease in chorea at lower frequencies. Lastly, Fawcett et al. [26] found similar clinical results with optimal stimulation being in the 70 Hz range. In this range their patient was found to have significant decrease in chorea, but also had improvement in voluntary saccades and improvement in his oculomotor deficits that were debilitating before surgery.

Not all studies have shown that optimal clinical control of the chorea without worsening of other motor symptoms is only found at lower frequency stimulations. Hebb et al. [27] found that bilateral DBS stimulation lead to a significant decrease in chorea initially and at 12 month follow-up, but found that rigidity continued to increase over that time frame and did not resolve with the stimulator turned off. Contrary to the findings of Moro et al., they found that step wise increase of the frequency of the stimulation up to 180 Hz lead to further increase in control of the chorea without deleterious effects on bradykinesia and rigidity. In a study of control of chorea as well as involuntary vocalization in the setting of HD, Gracia-Ruiz et al. [28] found that the use of a frequency of 130 Hz lead to optimal control of chorea and the debilitating involuntary vocalizations without worsening of bradykinesia.

Six studies have reported the long-term follow-up on patients treated with GPi DBS in refractory HD. Biolsi et al. [29] reported continued suppression of chorea over a 4 year follow-up period with stimulation at 130 Hz. The frequency settings remained the same over the follow-up period, and there was a clear return of chorea when the DBS was turned off at all follow-up intervals. Kang et al. [30] performed a similar long-term follow-up in a series with two patients and found that both patients had a significant reduction in chorea over the 2 year period with high frequency stimulation at 160 Hz. One of their patients did develop worsening of bradykinesia and dystonia over the follow-up period, but did not