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An Examination of Mobile Spinal Cord Stimulators on Treating Parkinson Disease

Zhen-Jie Wang, Takao Yasuhara¹

Abstract:

In animal models of Parkinson disease (PD), spinal cord stimulation (SCS) exhibits neuroprotective effects. Recent advancements in SCS technology, most importantly mobile stimulators, allow for the conventional limitations of SCS such as limited stimulation time and restricted animal movements to be bypassed, offering potential avenues for improved clinical translation to PD patients. Small devices that could deliver continuous SCS to freely moving parkinsonian rats were shown to significantly improve behavior, preserve neurons and fibers in the substantia nigra/striatum, reduce microglia infiltration, and increase laminin-positive area of the cerebral cortex. Through possible anti-inflammatory and angiogenic mechanisms, it has been demonstrated that there are behavioral and histological benefits to continuous SCS in a time-dependent manner. This review will discuss the benefits of this technology as well as focus on the limitations of current animal models.

Keywords:

6 hydroxydopamine, electrical stimulation, neuroinflammation, neuroprotection, Parkinson disease

Introduction

Parkinson disease (PD) manifests in the nigrostriatal system as a chronic neurodegenerative disease arising from the destruction of dopaminergic (DA) neurons. Bradykinesia, rigidity, resting tremors, and postural instability are the cardinal signs of PD. The first-line therapy for PD is levodopa treatment. Long-term pharmacological treatment, however, often results in adverse events, including dyskinesia and motor fluctuations.

loss of DA neurons in the substantia nigra pars compacta (SNc).^[1-3] DBS, however, involves an invasive surgical procedure which damages brain tissue and involves a permanent implant of a stimulator device. Intracranial hemorrhage risk in DBS is estimated to range from 0.8% to 2.8%.^[4-8] In addition, the effectiveness of DBS tends to be beneficial only in cases of motor fluctuations responsive to levodopa therapy, thus only limited amounts of PD patients are eligible for DBS.

Deep Brain Stimulation for Parkinson Disease

Deep brain stimulation (DBS) in advanced PD patients significantly enhances motor symptoms. DBS may increase BDNF in the animal models of PD and may prevent the

Spinal Cord Stimulation

The stimulation of the spinal cord in the treatment of intractable neuropathic pain shows a solid track record of success and protection. While not directly targeting lesioned areas, peripheral nerve electrical stimulation, such as facial nerve stimulation, has been shown to have therapeutic benefits for ischemia through vasodilation.^[9] While neurological injuries are the most severe complications of spinal

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Department of Neurosurgery and Brain Repair, Morsani College of Medicine, University of South Florida, Tampa, FL, USA, ¹Department of Neurological Surgery, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Okayama, Japan

Address for correspondence:

Dr. Takao Yasuhara,
Graduate School of Medicine, Dentistry and Pharmaceutical Sciences,
Okayama University,
Okayama, Japan.
E-mail: tkoyasuhara@hotmail.com

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cord stimulation (SCS), they have a low occurrence with a rate of 0.6%.^[10] In PD animal models, SCS decreases motor defects and protects dopaminergic neurons in the nigrostriatum.^[11,12] Electrical stimulation of the spinal cord, particularly at low frequencies, conferred therapeutic benefits by increasing neuroplasticity in PD models.^[13] In advanced PD patients with lumbago and leg pain, SCS has beneficial effects on motor control including improved balance, posture stability, and gait.^[14]

Animal Models of Spinal Cord Stimulation

In PD animal models, electric stimulation of the spinal cord is a successful modality for treatment. Technical issues, however, limit animal models of SCS such as short stimulation times (no more than 1 h a day) and minimum allowable free movement of animals (i.e., because of anesthesia).^[1-3,12,15-17] With the advancement of small mobile stimulators, it is now possible for freely moving parkinsonian rats to be treated with sustained DBS.^[18,19] These limitations of preclinical SCS animal models may be overcome in the translation to a clinical setting by repurposing preexisting small mobile DBS stimulators for usage in SCS. In a recent study, small mobile devices for continuous SCS in freely moving parkinsonian rats were developed.^[20] The research demonstrated both an effective delivery of SCS by a small mobile device and a time-dependency on neuroprotective effects of rats of the PD. Both groups of SCS treated rats typically had improved performance in both contralateral bias and methamphetamine rotation tests; however, the 24-hour stimulation group exhibited better therapeutic effects than the 8-hour stimulation group. Compared to rats in the control group, both the lesioned striatum and SNc exhibited significantly decreased microglial cells with the longer continuous SCS regime.

Small Mobile Devices for Continuous Spinal Cord Stimulation

Traditional SCS machines have allowed minimal parameter control for stimulation and greatly restricted animal movement. Present SCS devices consist of a large electric stimulator and an electrode which is implanted in wired animals.^[1-3,12,21-23] The long-term adhesion of wires into the skin can cause erosion or infection of the animals. Furthermore, free movement of animals is highly restricted through regular use of anesthesia while supplying SCS.^[12] The intrusive aspect of the current SCS procedure is likely to change experimental outcomes. The duration and timing of electrical stimulation remain limited to traditional SCS, given the large size of stimulators, hard-wired connections between stimulator and electrodes, use of anesthesia, and invasive operations.

The technological limitations for current SCS machines can be bypassed through a compact mobile electric stimulator. Such a system has already been demonstrated to be effective for DBS in PD animals and now a lightweight, continuous SCS mobile device has also been developed.^[18-20] This method achieves minimum invasiveness, free movement with a wireless system, readily accessible adjustment of stimulation conditions, and robust, stable stimulation in PD animals for at least 2 weeks [Figure 12]. Of note, Bluetooth signaling efficiently controlled stimulation parameters. By expanding the use of the small mobile device originally used in DBS to SCS, a which through an epidurally implanted electrode achieves a less invasive procedure and modality than targeting the deep areas of the brain (e.g., thalamus, subthalamic nucleus, and globus pallidus). It is feasible that SCS will be used to respond in real time and in a graded manner to an individual's unique disease state through a closed-loop stimulation system containing both stimulation and receiving functions. In view of technical advances in downsizing and wireless communication, such a handheld SCS system will possibly be available in the near future.

Improved Therapeutic Outcomes in Parkinson Disease Animals with Prolonged Spinal Cord Stimulation

Although PD animals have been reported in neuroprotective effects of SCS, the optimal condition for electrical stimulation remains uncertain. Parameters such as pulse width (400-1,000 μ s), frequency (300-333 Hz), and stimulation duration (30 min at two times/week, for 4.5%-30 min at a time each week for a span of 5 weeks) for effective electrical stimulation in rats all vary widely.^[16,23] The ideal conditions for the SCS short burst have previously been identified as follows: Pulse width, 100 μ s; frequency, 2, 50, and 100 Hz; and stimulation duration, 1 h for 16 consecutive days.^[12] For the "continuous" approach to SCS, the ideal frequency has been identified as 50 Hz. Based on two groups with a stimulation duration of 8 h versus 24 h, the time dependency of SCS has also been found. Whilst behavioral improvement, TH-positive nigral neuron survival, and angiogenesis level did not differ between 8 and 24-h stimulation groups, the longer SCS retained more striatal TH fibers than the shorter SCS treatment and exhibited a higher degree of anti-inflammatory impact. The diminished activation of microglial cells by sustained SCS therapy indicates that gradual detrimental neuroinflammation can accompany PD, requiring sustained treatment to isolate cell death pathways effectively.^[20]

Spinal Cord Stimulation Anti-Inflammatory Effects

Neurodegeneration of PD manifests itself partly as a chronic neuroinflammation characterized by activated

microglial cells in the striatum and SNc.^[24] In the case of normal Sprague-Dawley rat, electrical stimulation may modulate neuroinflammation – DBS therapy significantly reduces activated microglia surrounding electrodes.^[25] In animal models of spinal cord ischemic reperfusion injury, studies have shown that SCS treatment also stimulates anti-inflammatory responses and reduces microglial activation through downregulation of the ERK1/2 pathway, a signaling mechanism backed by pain studies.^[26-31] Researchers further found that following intrastriatal 6-hydroxydopamine (6-OHDA) administration in the 24-h stimulation group, SCS decreased the number of microglia cells through anti-inflammatory effects likely exerted through signaling pathways from dorsal column-medial lemniscus, propagating into the SNc and striatum.^[20] The study of this system of anti-inflammatory signaling requires further electrophysiological tests.

Spinal Cord Stimulation Enhances Angiogenesis

Cervical low-frequency SCS enhances brain flow in the cerebrum and lasts for at least 15 min after SCS is discontinued.^[32-34] However, there have been no previous reports correlating cerebral blood vessel vasculostructural changes and SCS. Researchers found that SCS increased the laminin-positive areas within lesioned areas of brain cortex.^[20] These findings indicate that intrastriatal transplantation in PD rats of the encapsulated vascular endothelial growth factor (VEGF) secreting cells enhances angiogenesis.^[35] In the case of PD rats receiving sporadic SCS (1 h/day 7 consecutive days), these results parallel the upregulation of in VEGF in a lesioned striatum.^[12] The fact that SCS modulates unique growth factors associated with vasculature implies a connection between electrical stimulation and secretion of growth factors, which may mediate the observed increase in the laminin-positive vascular region of SCS-treated PD rats in the cerebral cortex.^[36-40]

Spinal Cord Stimulation Clinical Application in the Future for Parkinson Disease

In PD pathogenesis, neuroinflammation can include multi-pronged neurodegenerative processes, such as inflammation and neurotrophic factor downregulation.^[12,35,41-43] In other neurological diseases such as stroke, traumatic brain injury, Huntington's disease, and peripheral nerve injury, this neurodegeneration, characterized by aberrant inflammation and dampened neurotrophic factor levels, manifests itself as a key secondary cell death pathway that may be a potentially potent therapeutic target.^[44-48] The potential of SCS to limit these secondary cell death

pathways should be further probed for insights into optimizing therapeutic outcomes and the understanding the mechanism of electrical stimulation.

In advanced PD patients, DBS provides an important therapy for motor symptoms. Compared to DBS, SCS is less invasive in that the procedure spares the brain from surgical manipulations. In reducing the hallmark PD motor deficits, such minimally invasive SCS may be as successful as DBS. Indeed in PD marmosets, SCS relieves motor deficits.^[21] Despite promising results in animals, however, a case report revealed that SCS in two PD patients failed to alleviate akinesia or restore locomotion, raising questions on efficacy in humans.^[49] Based on available information, the therapeutic benefits of this minimally invasive electrical stimulation should be enhanced by the optimization of SCS through the use of continuous stimulation provided by a small mobile stimulator.

Limitations

The study examining mobile SCS stimulators used the PD form of 6-OHDA-induced rats for analysis.^[20] The key benefits of this model are the simplicity of developing the lesion that induces loss of striatum dopaminergic fibers and substantia nigra dopaminergic neurons; however, there is a key drawback of this model in that it does not resemble the normal pathology of PD, which is a gradual development of nigrostriatal dopaminergic neuron degeneration through alpha-synuclein degradation. Other PD models of neurodegeneration and alpha-synucleinopathy should be investigated to further evaluate the therapeutic value of the SCS.

The neuroprotective effects of continuous SCS were examined with the goal of treatment length as a key factor. Therapy was begun shortly after the creation of 6-OHDA lesions, which may not be applicable in the clinical setting, as the signs of PD do not occur until at least 80% of the dopaminergic neurons have been exhausted.^[20] Further research in this area will most likely involve testing SCS in a late-stage PD model. Another drawback is that further investigation will be required to elucidate the therapeutic function of SCS. Research exhibited that angiogenic potentials triggered neuroprotective effects, but whether the neuroprotective effects of SCS during the presymptomatic phase are maintained during the symptomatic phase requires further review. In the future, behavioral changes postdiscontinuation of SCS may uncover the mechanisms of action on PD symptoms as well as the long-lasting effects of SCS.

Conclusion

Small mobile stimulators can provide continuous SCS and in a time-dependent manner exert neuroprotective effects

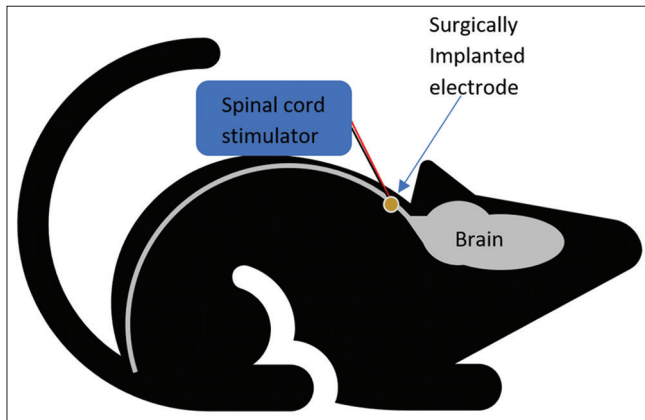


Figure 1: A mobile spinal cord stimulator can be used to deliver continuous electrical spinal cord stimulation with settings that can be adjusted wirelessly for maximal therapeutic effect on Parkinsonian rats. Electrodes are placed in the spinal cord rather than in the deep brain nuclei, which prevents complications of more invasive intracranial surgery

in PD rats. SCS attenuates both behavioral and histological deficits associated with symptoms of 6-OHDA-induced PD, likely through mitigating the activation of microglia while simultaneously strengthening angiogenesis. Through further understanding of the interplay through electrical stimulation, neurodegeneration, and neuronal reconstruction, the mobile stimulator system for continuous SCS provides significant utility both as a valuable instrument for basic science and also as a potentially useful therapeutic modality for PD.

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Conflicts of interest

There are no conflicts of interest.

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