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ELECTRICAL STIMULATION METHODS FOR THE PRECLINICAL TREATMENT OF TBI SEQUELAE – AN OVERVIEW

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Abstract— *Electrical stimulation methods have been used in numerous studies to treat a variety of neurologic disabilities. Traumatic brain injury (TBI) may lead to several different complications, many of which can be treated with electrical stimulation. Only recently, the focus of researchers has shifted more towards preclinical studies to be able to investigate the underlying mechanisms of how these stimulation methods affect nervous tissue in greater detail. This article will give an overview of the most prominent electrical stimulation modalities, namely transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), deep brain stimulation (DBS) and vagus nerve stimulation (VNS). Some preclinical studies will be highlighted to show the diverse range of possible applications of electrical stimulation for the treatment of TBI sequelae.*

Keywords— *traumatic brain injury, transcranial magnetic stimulation, transcranial direct current stimulation, deep brain stimulation, vagus nerve stimulation*

Introduction

Traumatic brain injury (TBI) may lead to a variety of different diseases and disabilities, ranging from neuropsychiatric changes to motor impairments [1]. Neuropsychiatric sequelae can be subdivided into cognitive disorders, such as attention, memory and executive deficits, and behavioral disorders like personality changes, depression, anxiety and posttraumatic stress disorder [2]. Post-TBI motor impairments include tremor, ataxia, paresis and postural instability [1]. TBI patients are also prone to headaches, dizziness, nausea, fatigue, sleep disturbances and seizures [2].
Over the years, many different therapeutic methods have been proposed to target neuronal damages caused by TBI at various stages post-injury. A modern approach is the stimulation of neurons with the help of electrical currents to mitigate further damage following the initial incident and help restore original function in the affected areas [3]. This article will give a brief overview of the most commonly used methods for electrical stimulation of nervous tissue and different stimulation protocols that can be applied. The aim is to provide a basis for finding new treatment modalities and an incentive to refine stimulation parameters of existing protocols for specific disabilities to achieve better treatment outcomes.

Effects of Electrical Stimulation

Nervous tissue can generate action potentials spontaneously based on the intrinsic properties of the neuronal cell membranes. The excitability of neuronal cells allows for the modulation of their activity through neurostimulation. The resulting activation or inhibition of excitable tissue may serve as an effective therapeutic method in many subfields of neurology, especially in neurotraumatology [4].
The effect of electrical stimulation depends on intrinsic features of the targeted brain tissue. On a neuronal level, it is generally easier to excite an axon than a soma, while myelinated axons are the most excitable part of the cell [3]. In almost all cell areas, except for some types of dendrites [3], action potentials can be elucidated easier with negative currents. Increasing the negative potential of the extracellular space drives depolarization within the neuron, which can ultimately lead to the induction of action potentials. Branching, bending and diameter changes of the axon lead to differences in the site and threshold of the stimulation [3].
Electrical stimulation influences brain electrophysiology on a deeper level through modulation of neuronal signaling. This effect is not only limited to short-term observations, but can also result in the facilitation or attenuation of long-term modifications on a cellular level. Activity-dependent synaptic plasticity may either strengthen or weaken the formation of synapses, which is crucial for post-traumatic regeneration and recovery of high-level cognitive abilities like learning and memory formation [5].
Since TBI may result in a lower threshold to seizures [4], the safety of electrical stimulation needs to be considered. Only very few studies, however, report seizures after stimulation of brain tissue of TBI patients, which may correlate with the severity of the injury [4].

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Stimulation Methods

Transcranial Magnetic Stimulation (TMS)

TMS utilizes magnetic fields to induce electrical currents in cortical tissue with the aim to improve various neurologic conditions. A magnetic coil is positioned tangentially near the surface of the head of a subject, acting as the stimulating device. Discharging a large alternating electric current through the coil leads to a magnetic field perpendicular to the stimulating coil. This magnetic field is able to penetrate the skull and induce secondary electrical currents in the intracranial tissue [6]. Depending on the direction of the induced current, the change in membrane potential may result in the inhibition or excitation of neuronal activity, as well as the elicitation of action potentials when the cell membrane is depolarized above its threshold potential [6].
Since the induced electromagnetic field diminishes greatly over distance through the neuronal tissue, TMS is mainly used to stimulate structures near the surface of the brain such as the neocortex. Some of these structures project axons to deeper regions within the brain, allowing for indirect stimulation of functionally connected regions [7]. Different coil types achieve different penetration depths depending on their geometry, materials, and coil design. Circular coils achieve a higher depth penetration and are used to stimulate larger volumes of neuronal tissue since the entire region below the coil is affected similarly. A figure-of-eight shaped coil, where two circular coils are positioned next to each other with their currents flowing in different directions, allows for more selective stimulation of brain tissue at the cost of stimulation depth. The intersection of the two electromagnetic fields produced by this arrangement is characterized by an increased current density compared to the surrounding regions [6]. TMS can be applied in the form of single or repetitive pulses [8], leading to different treatment outcomes.

Transcranial Direct Current Stimulation (tDCS)

tDCS uses direct current, as opposed to the pulsed protocols of most other stimulation methods, to hyperpolarize or depolarize the membranes of neurons in desired cortical areas [9]. For that, two large pad electrodes are placed on the scalp of the patient near the area of interest and a current of several milliamperes is applied. Thereby, the current density is the decisive factor for the efficacy and localization of the induced stimulus [10]. The resulting excitation or inhibition of neurons can lead to neuromodulation [9].
This stimulation method is painless, noninvasive, and can be used as a treatment for depression and a variety of cognitive dysfunctions, including TBI sequelae [11]. Anodal tDCS increases the excitability of underlying cortical neurons, while cathodal tDCS inhibits neuronal activity [10].

Deep Brain Stimulation (DBS)

DBS involves the implantation of a stimulation electrode into a target brain region so that electrical stimuli can be delivered to specific brain areas. It is commonly used for the treatment of Parkinson's disease, essential tremor, obsessive compulsive disorder and epilepsy in humans [12]. Due to its versatility and accuracy, DBS has potential as a treatment for many different neurological diseases, including sequelae from TBI. The targeted area depends highly on the kind of condition to be treated. Current research focuses on neuromodulation and the neuroprotective effects of DBS, as well as its potential for neurogenesis [13].
DBS systems usually consist of a stimulation electrode that is implanted in the target area and a connected subcutaneous wire that forwards the stimuli from an external pulse generator. Stimulation electrodes are frequently implanted bilaterally and comprise four metal contacts, which can be used both as anodes and cathodes [13]. Bipolar configurations, where an electrical field is generated between two adjacent contacts, allow for a concentrated electric field and higher precision.
The brain area of interest is usually identified with the help of CT and MRI scans, which may also be used to guide the surgeon during implantation. During the procedure, electrical activity is continuously measured through the DBS microelectrodes to determine their relation to the target area and verify the position of the metal contacts. Afterwards, initial stimulation is carried out to confirm the efficacy of the implanted device. [14]

Vagus Nerve Stimulation (VNS)

VNS is an invasive stimulation method that uses a cuff electrode wrapped around the vagus nerve to indirectly stimulate distant brain regions. The United States Food and Drug Administration (FDA) has approved VNS for the treatment of drug-resistant epilepsy and refractory major depressive disorder. Several studies show that it may also be useful in the treatment of TBI sequelae. The exact mechanisms underlying VNS are still not fully understood, but several studies have revealed its potential for neuroprotection, which is achieved through a combination of anti-inflammatory effects, reduction of the permeability of the blood-brain barrier and the modulation of neurotrophins and neurotransmitters [15]. Preclinical research focuses on various applications for VNS and further investigations into its underlying mechanisms. It has been shown that it is able to mitigate TBI sequelae in animal models and is therefore a promising new treatment approach.
Most commonly, the stimulation is delivered to the left cervical vagus nerve [16], which is relatively easy to access through surgical means. Stimulation of the right vagus nerve is usually avoided since it has more projections to the cardiac atria and could therefore

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affect the cardiac rhythm [16]. Helical electrodes, which can have a monopolar, bipolar or tripolar configuration, are implanted and wrapped around the vagus nerve. Monopolar electrodes are comparatively cheap but require an additional ground electrode. Bipolar configurations allow the induced current to flow between the two electrodes, enabling a much greater control of the current path. Tripolar electrodes are more expensive, but this configuration can prevent leakage currents by positioning the stimulating electrode between two common counter-electrodes.

Treatment Outcomes

The stimulation methods mentioned above are under preclinical investigation to treat a variety of conditions directly or indirectly related to TBI. Not just the modality of stimulus delivery, but also the stimulation protocol is of utmost importance to reach the desired outcome. Factors such as stimulation frequency, amplitude and signal shape have different effects on the affected tissue, and finding the optimal parameters is often an iterative process. Additionally, researchers are interested in the time frame of the treatment, which includes the optimal time for the onset of stimulation after TBI and the number of sessions per day, or whether the stimulation delivery is connected to a trigger during behavioral tests. This section highlights some examples of preclinical studies using electrical stimulation to treat TBI sequelae.

In [17], researchers use TMS together with environmental enrichment to facilitate recovery from TBI by increasing cortical excitability and reorganization. Rats are subjected to a controlled cortical impact (CCI) TBI model and stimulated for six days with custom 25 mm figure-eight TMS coils placed above the center of their head between the lambda and bregma. Stimuli are delivered once daily with the following protocol: 7 cycles of 4 s, 26 s interval between stimuli, 10 Hz pulses. After six weeks of behavioral and functional tests, the investigators concluded that the TMS group showed a significant improvement on the beam walk and challenge ladder tests, as well as increased primary somatosensory cortex local field potentials and biceps motor evoked potentials compared to an unstimulated control group.

As an example of a tDCS study, [18] describes a stimulation protocol to decrease impulsivity in a rat TBI model using CCI. Before CCI, the animals were trained on a five-choice serial reaction time task to measure their motor impulsivity and attention. After injury, rats were allowed to recover for 6 weeks before tDCS sessions began. While the rats were anesthetized, two Ag/AgCl hydrogel electrodes were placed on their heads for stimulation, with the cathode in front of the bregma and the anode between the scapulae. tDCS session were carried out daily over a period of 7 days in the form of cathodic stimulation for 10 min with 800 µA, resulting in a current density of 7.08 A/m². Two hours after stimulation, tests were started and the results compared to the post-injury baseline that was acquired after the recovery period. It was found that cathodal tDCS slightly decreased accuracy, but significantly reduced impulsivity in the reaction time task compared to the unstimulated baseline, with the greatest recovery in rats with more severe deficits.

Rajneesh et al. [19] demonstrate the effect of DBS on bladder function of rats with TBI induced by the weight-drop method. Four weeks post-injury, twisted bipolar DBS electrodes were implanted in the pedunculopontine tegmental nucleus (PPTg) of the animals. Thereafter, an initial urodynamic measurement was conducted to evaluate bladder function. Electrode positions were verified with the help of MRI studies. During experiments, the bladder contraction pressure was continuously measured. When it exceeded a given threshold, DBS with a frequency of 50 Hz, a pulse width of 182 µs and varying voltages between 1 and 2.5 V was applied for 10 s to augment bladder contractions. Urodynamic analyses showed that the DBS protocol with 2 V significantly improved the voiding efficiency of TBI rats from 39 to 69 %. They concluded that DBS in the PPTg is an effective treatment for bladder dysfunction.

In [20], the wake-promoting effects of VNS are investigated. Adult rats were subjected to a severe TBI model by free fall drop and their degree of consciousness was observed one hour later. Thereafter, the left vagus nerve was surgically exposed at the cervical level and a VNS electrode wrapped around it. Animals were then stimulated by a VNS protocol with a frequency of 30 Hz, an amplitude of 1 mA and a pulse width of 0.5 ms. Their consciousness was assessed again one hour after stimulation. Six hours after VNS, rats were euthanized and tissue from their prefrontal cortices extracted for further immunohistochemistry and western blot analysis. These findings were compared with observations from unstimulated rats, and the researchers concluded that VNS could promote alertness, with the primary mechanism being the upregulation of excitatory and the downregulation of inhibitory neurotransmitters.

Conclusion

From the examples shown above, it is apparent that electrical stimulation can be used to treat a wide variety of neurological impairments. Although electrical stimulation methods differ greatly in the way the stimuli are delivered, the underlying mechanisms to induce neuronal modulation are often quite similar. Investigating these mechanisms and comparing them between different stimulus delivery modalities could lead to new neurological insights and aid in the discovery of innovative concepts for electrical stimulation. The main objective is to find novel stimulation methods that are less invasive and more precise than current approaches.

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