MAYO CLINIC

Optical Stimulation for Restoration of Motor Function After Spinal Cord Injury

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Abstract

Spinal cord injury can be defined as a loss of communication between the brain and the body due to disrupted pathways within the spinal cord. Although many promising molecular strategies have emerged to reduce secondary injury and promote axonal regrowth, there is still no effective cure, and recovery of function remains limited. Functional electrical stimulation (FES) represents a strategy developed to restore motor function without the need for regenerating severed spinal pathways. Despite its technological success, however, FES has not been widely integrated into the lives of spinal cord injury survivors. In this review, we briefly discuss the limitations of existing FES technologies. Additionally, we discuss how optogenetics, a rapidly evolving technique used primarily to investigate select neuronal populations within the brain, may eventually be used to replace FES as a form of therapy for functional restoration after spinal cord injury.

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Despite efforts to elucidate the pathophysiology of spinal cord injury (SCI) in the past few decades, the search for a cure continues.[1-3] Currently, the criterion standard of care is to provide intense physical rehabilitation after the acute injury phase in an attempt to maximize any spontaneous recovery of respiratory, hand, arm, leg, bowel, bladder, and sexual function.[4] Although this paradigm increases the possibility of some degree of recovery, particularly in patients with incomplete injuries, most patients do not experience a full recovery and have only limited gains with current rehabilitation therapy.[4-7]

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The poor chance of recovery after SCI has inspired a substantial amount of research aimed at restoring lost function in SCI survivors. From a biological standpoint, these efforts have primarily focused on molecular manipulations to lessen the degree of secondary injury that occurs via ischemia and excitotoxicity,[5,8-14] replacement of lost neurons and glia via stem cell transplant,[15,16] and remyelination or axonal regeneration by either reducing glial scar formation[17] or by inserting biomaterial substrates[18] that promote neural regrowth.[19-23] Unfortunately, these approaches have been met with limited success because of the complexity involved with degrading glial scarring while regenerating neural tissue and directing appropriate neural connections required to restore severed spinal pathways.[24]

An alternative to molecular manipulations is to activate remaining neuromuscular components, which, despite the loss of descending input, can still be activated via external stimuli. Historically, the most common form of stimuli has been electricity. Namely, functional electrical stimulation (FES) has been successfully used to restore breathing,[25,26] lower[27-29] and upper[30,31] extremity function, and bladder and bowel control.[32-35]

Presently, FES systems can restore lost function, but they have a narrow scope of application and generally only restore one previously lost function at a time. For example, phrenic pacing has allowed individuals with high cervical injuries and intact phrenic nerves to successfully wean from mechanical ventilation, leading to increased survival rates and improved quality of life.[36,37] Additionally, Parastep (Sigmedics, Inc), a commercially available device that relies on surface stimulation of the quadriceps, gluteal muscles, and peroneal nerves, permits individuals with lower SCI to ambulate for distances of more than a quarter of a mile.[38] Furthermore, the Vocare bladder control system (Finetech Medical) utilizes anterior sacral root stimulation to restore micturition.[39,40]

Despite the proven effectiveness of these systems, technological shortcomings and practical limitations such as inadequate activation control strategies,[41] electrical current spillover,[42-44] and muscle fatigue[45] have led to a limited integration of FES systems into the daily lives of SCI survivors.[41] Optogenetics, a novel stimulation modality that uses light to either excite or inhibit genetically modified neurons, has the potential to overcome some of the limitations facing current FES strategies.[1,46,47]

OPTOGENETICS

Optogenetics is a rapidly evolving technique originally developed to study neural activity in select neuronal populations.[48] The genetic material of specific cell populations is modified via viral vectors to express a transmembrane protein reactive to light (opsins). These transmembrane proteins undergo a conformational change when light of a specific wavelength (390-700 nm) is applied directly to the cells, resulting in selective ionic current flow across the cell membrane. In turn, positively charged (cations) or negatively charged (anions) ionic movement will lead to cell depolarization or hyperpolarization, respectively. Therefore, specific viral vectors can be chosen and modified to transduce specific neuronal populations, allowing for selective modulation with light. Excitatory responses can be achieved by activating channelrhodopsin-2 (ChR-2) cation channels (responsive to 470-nm wavelength blue light), which allow entry of positively charged sodium and calcium ions into the cell (Figure 1, A).[50,51] In contrast, inhibitory responses can be evoked by activating halorhodopsin, a transmembrane ion pump, using 580-nm yellow light, which facilitates the movement of negatively charged chloride ions (Figure 1, B).[5,47]

The use of optogenetics has previously focused on characterization of neuronal mechanisms of excitation and inhibition within the brain.[5,8,10,12-14,52] However, increased interest in translational applications of optogenetics technology has resulted in the pursuit of novel clinical avenues for restoration of vision, seizure control, and treatment of cardiac arrhythmias.[19,53,54] Light offers clear advantages for modulating neuronal behavior. Specifically, optical stimulation can provide real-time, selective control of cellular activity.[51] Additionally, efforts to expand the toolbox for controlling neurons via light have led to an increased variety of ChR-2s that are altered to respond to various light wavelengths with enhanced ion channel kinetics and selectivity.[55] More recent efforts have led to the first light-gated chloride channel, engineered from the ChR-2 transmembrane family of proteins,