論 文 の 内 容 の 要 旨

Abstract

論文題目　High Resolution Spatiotemporal Optogenetic Spinal Cord Stimulation
（高時空間分解能光遺伝学的脊髄刺激）

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Spinal cord stimulation has long been used as a medical therapy to relieve neuropathic pain. It has also been studied as a research tool to treat motor dysfunction after spinal cord injury. The standard stimulation method involves the placement of electrodes on the epidural spinal cord and conduction of electrical current through them in order to change the neuronal activity. However, in the absence of a definitive cell-type selection and spatial resolution, it is difficult to determine the stimulation target, thereby rendering the underlying mechanism ambiguous.

To overcome these limitations, we aimed to focus on the development of a novel spinal cord stimulation system with high resolution and selectivity that can specify the stimulation target in rat models. Here, we propose to utilize optogenetics to design a spinal cord stimulation mechanism with high cell-type selectivity as well as a multichannel optical stimulation device that has a high spatial resolution.

As a realization of this concept, a Single Laser to Multiple Optical Fiber (SLMOF) device with 720 channels was developed. This system could provide a stimulation resolution 26.7 times higher than the previous research of electrical stimulation. By precisely controlling the projection of laser within the device, we can provide stable light outputs at a low cost.

In order to examine the details of light penetration and absorption on the spinal cord, we simulated the light propagation in a 3D spinal cord model by using a Monte Carlo-based light transport model. The simulation results revealed that a major portion of the light is absorbed in the vicinity of the surface of the spinal cord with some fraction spreading over the surrounding tissue. The data were also verified by *in-vitro* assessment of light penetration within spinal cord tissue slices. Compared to electrical

stimulation, which affects the neural activity in a broad region of the spinal cord, light strictly propagated in a restricted area within the nervous structure.

W-TChR2V4 transgenic rats that express the light-gated ion channel in mechanoreceptive and proprioceptive neurons of the spinal cord were used to validate the results. We also set up a spinal cord injury model for demonstrating the application of our device. In order to interface the optics to the animal model, we designed a novel spinal cord window.

Then we carried out a series of *in-vivo* experiments to evaluate our method and compare it with the existing electrical stimulation method. First, we confirmed that the optogenetic spinal cord stimulation could induce paralyzed muscle reaction after spinal cord injury. Then, we measured the EMG response latency of each stimulation, revealing that our epidural optical stimulation only directly affected the afferent neurons and interneurons on the dorsal part but not motoneurons. Also, analyzing the muscle-contraction-related stimulation spots on the epidural spinal cord indicated the capability of our system to stimulate different somatosensory pathways with greater selectivity in comparison to that of electrical stimulation.

Through this research, we demonstrated that our multichannel optogenetic spinal cord stimulation system can stimulate the somatosensory pathways in the spinal cord in rat models with a higher resolution and selectivity than in the case of an ordinary electrical stimulation setup. We plan to use the system to study how epidural stimulation modulates the functional output of the spinal cord during spinal cord injury. We believe that adopting this system would aid in our comprehension of the mechanisms underlying specific spinal cord responses during therapy post injury.