Commentary

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A new optogenetic device for spinal cord control of pain

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Pain research, like other areas of neuroscience, has seen many recent advances with the aid of optogenetics, a broadly enabling technique that allows researchers to activate or silence distinct cell populations.[1,5,7,13,15] To date, the majority of pain studies using optogenetics in freely behaving animals have focused on the periphery and brain but not the spinal cord.[9] This disparity has reflected the fact that the most widely available fiber-optic light delivery devices were designed for use in the brain, and thus were poorly suited for the unique anatomy of the rodent spinal cord. To address this challenge, in late 2015, a collaborative effort from Gereau and Rogers produced a fully implantable, soft wireless optical system that allowed for the first demonstration of spinal optogenetics in freely moving mice.[11] Following this proof-of-concept study, in this issue, Samineni et al.[14] report the development of an improved, commercially available wireless optoelectric device for spinal optogenetics.

Samineni et al.[14] designed their optoelectric device with simplicity and ease of operation in mind. The device consists of a rectangular shaped coil that serves as both an antenna and anchor, and flexible needle probe that possesses a micro-light emitting diode (μ-LED) at its tip. In contrast to the previous implantable device from the authors, which was entirely housed inside the epidural space,[11] the current iteration inserts only the small μ-LED probe into the epidural space and leaves the large coil transmitter on top of the vertebral column. This design thus minimizes the potential for damage to the delicate spinal cord tissue, reduces the likelihood of device failure, and facilitates the implantation procedure.

Wireless optogenetic systems required the use of specialized resonant chambers,[10] but the device from Samineni et al. can function in myriad apparatuses simply by creating an external double loop antenna along the perimeter of the container. This important feature will allow pain researchers to flexibly apply this device in diverse assays with the potential for multiplexing. To demonstrate that their device could reliably perform under realistic conditions, Samineni et al. conducted a series of tests. To assess light output, the device was placed at 27 positions within a V-maze. At all positions, the light output of the μ-LED remained stable. To assess the effects of mechanical strain, the antenna coil was bent to a 5-mm radius of curvature. Even under this extreme condition, the performance of the device was negligibly affected. Notably, the device still functions 3 weeks after implantation, which offers the possibility for long-term experiments.

Importantly, to demonstrate the ability of their system to manipulate spinal circuits, Samineni et al. used the wireless optoelectric device to activate spinal afferents expressing channelrhodopsin (ChR2) in TRPV1-lineage neurons (TRPV1-ChR2). Mice lacking ChR2 were used as controls. Because TRPV1-lineage neurons represent the majority of nociceptors,[3] the authors hypothesized that turning the light on would elicit nocifensive behaviors such as licking, biting, and jumping in the TRPV1-ChR2 animals but not the controls. Consistently, they found that illumination caused the TRPV1-ChR2 mice to exhibit a substantial increase in nocifensive behaviors compared to baseline, while the control mice showed no difference. To further demonstrate the utility and flexibility of their system, Samineni et al. conducted a real-time place aversion assay in which 1 arm of a V-maze apparatus turned the μ-LED on, while the other arm turned it off. As predicted, the TRPV1-ChR2 mice showed dramatic aversion to the "light-on" arm, while control mice spent equal time in both arms.[14]

With the capabilities of this device now evident, the potential applications for pain research are broad. This study and the previous study by Park et al.[11] used the epidural devices to activate primary sensory afferents expressing ChR2. However, to realize the full potential of this system, future studies should also aim to optogenetically manipulate the resident neurons and nonneuronal cells of the spinal cord. It will also be important to demonstrate that the wireless μ-LED is capable of driving inhibitory opsins such as halorhodopsin or archaerhodopsin. Chemogenetic tools such as DREADDs have been successfully applied to manipulate spinal cord cells.[12] Combining the wireless devices from Samineni et al. with chemogenetic tools would allow researchers to manipulate multiple cell types simultaneously, offering unprecedented insights into complex circuitry in the spinal cord. Wireless light delivery to the spinal cord can also serve other uses besides manipulating opsins. For example, with an ultraviolet μ-LED, the wireless device could be used to permanently label activated neurons during complex pain behaviors using the novel calcium integrator CaMPARI.[6] Similarly, the blue μ-LED presented in this study could be used with the recently developed *i*Tango system to access spinal cells that are under the control of G protein-coupled protein -linked neuromodulators such as dopamine or neuropeptides (eg, somatostatin and proenkephalin).[8] These are but a few of the many ways that this new technology will empower future pain researchers using optogenetics.

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Some outstanding questions remain. Will the devices remain functional for longer term studies (>3 weeks) and would they eventually cause tissue damage? Can neurons in the deep dorsal horn, or even the ventral horn, be efficiently manipulated with the wireless devices? How does the performance of the wireless system compare to optogenetic stimulation from conventional fiber-optics in the spinal cord.[2,4] And will the new technology be sufficient to produce central sensitization phenomena such as wind-up or long-term potentiation that can be produced with traditional electrical stimulation? Future studies will hopefully address these questions and clearly define the advantages and limitations of this system.

In summary, Samineni et al. have developed a novel wireless device for opotogenetic manipulation of spinal cord circuits. Successful application of this device to spinal cord research by other groups will significantly expand our knowledge of the spinal cord and may also lead to new treatments for pain, itch, and motor diseases.

Conflict of interest statement

The authors have no conflict of interest to declare.

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