Novel OptoGPCRs open new avenues in optogenetic modulation

Sunday's Neurotechnology Plenary detailed how optical technologies can lower invasiveness and improve effectiveness in treating neurological disorders such as Alzheimer's, epilepsy, and migraines.

Ofer Yizhar. Credit: Ronen Goldman.

Anyone who has ever suffered a migraine or a cluster headache almost certainly recalls wondering, amid an excruciating episode, why the pain can't just stop. One of Sunday's Neurotechnology plenary speakers, Dr. Ofer Yizhar, believes that by literally shining some light on the subject, it can.

Yizhar presented in the afternoon's Neurotechnology session, where, like Dr. Daniel Razansky of the University of Zurich in a separate talk, he described methods that could dramatically reduce invasiveness and side effects of brain procedures. Between them, they hold promise for treating a wide range of conditions.

Dr. Yizhar is working on an optical technology that projects red wavelengths to dampen hyperactive brain neurons associated with pain and other conditions, such as epilepsy. The light induces those neurons to shut down, thus halting the pain, or the seizure. It is a novel approach to optogenetics — the discipline of combining photonics with gene modification.

In conventional optogenetics used for other purposes, blue wavelengths trigger ions to travel along channels in a neural network. This flow persists for as long as the light shines on the neuron. But once the light is switched off, this ionic current ceases.

Ofer Yizhar (left) and PhD student Daniel Zelmanoff in safety goggles as they work on a new approach for deep-brain light targeting. Credit: Ofer Yizhar.

Yizhar, a professor of brain sciences at the Weizmann Institute of Science in Rehovot, Israel near Tel Aviv, is not using blue light. Nor is he using the on/off channel-based method, as he explained in his talk, "High-sensitivity optogenetic silencing with novel OptoGPCRs."

Instead, he is aiming red light at genetically modified neurons that, when stimulated only once by the light, reduces their signals. That's because the genetic portion of his optogenetics modifies the neurons with an optically sensitive protein type known as a GPCR, which stands for G-protein-coupled receptors. By their nature, optoGPCRs, when stimulated by light, do not activate conventional ion channels. Rather, they trigger the activity of what's known as G protein pathways. Yizhar's GPCRs are also known as opsins.

Like an on-off switch

"The channel-based optogenetic tools are like an on/off switch," says Yizhar. "You have light, it switches on. With no light, it switches off. Whereas with the GPCR pathway, the light kind of activates the process, and the process keeps going even after the light is switched off. It basically keeps going for a longer time in the dark."

This might sound like a way to stimulate a neuron, and it well could be. But in Yizhar's case, he is using the technology to deactivate neurons that are hyperactive, leading to aberrant brain activity.

"Turning on neurons is relatively easy," notes Yizhar, who points out that electrodes attached to the brain will do the trick. "Causing neurons to stop spiking is a much more difficult process."

Among the challenges of using conventional, channel-based optogenetics for shutdowns: "If you want to shut everything off, then you need to constantly deliver the light into the brain," Yizhar says. "If your opsin is like a channel — if it kind of closes when the light goes out — then you need the light to be always on. The reason why these GPCR pathways are useful is because they keep cycling, even after you shut down the light. So you can have a long lasting effect without having to pump so much light into the tissue."

But what would be so wrong with constantly pumping light into the brain?

"It causes all kinds of artifact — heating, damage, photoxicity, all kinds of things that we don't like to have," explains Yizhar. To pick up on one of those undesirables: photoxicity is basically a chipping away of the brain instigated by neurons absorbing photons.

Yizhar adds that the amount of light required for his G protein pathway approach compared to the "channel" method is "about four orders of magnitude less, so 10,000 fold less light."

While the G protein method is new, it is not the only innovative aspect that Yizhar is deploying to minimize the amount of light. His use of red wavelengths rather than blue also plays a big role.

The comparatively longer wavelength of red "heats the brain tissue less than the shorter wavelengths do," say Yizhar. "And it travels better through the tissue. One red photon will travel about 10 times more through the brain tissue than a blue photon before it's absorbed or scattered. The interface with biological tissue is much better with red light."

To facilitate red, Yizhar — again, on the genetic side of the optogenetic tandem — is infecting neurons with the red sensitive OPN3 gene from a mosquito. Earlier blue methods infect neurons with a blue sensitive gene derived from algae.

The OPN3 gene will sit in the neuron doing nothing, until red light springs it into action.

Yizhar's technology holds great promise for treating brain disorders linked with hyperactivity of neurons, including epilepsy, movement anomalies, and pain.

"Most of the disorders of the brain are disorders of hyperactivity, and for many of them we have no effective therapy" says Yizhar. "So this is why having an efficient inhibitory optogenetic tool that can shut down processes when they're happening in an unwanted way is really useful."

Yizhar and his team began developing the technology at Weizmann in 2016, and have proven its effectiveness in mice. One of the remaining challenges is to scale up the process so that it works reliably on larger brains, such as a human's.

A breakthrough in that direction came in 2023, when Yizhar and his team collaborated with the Rochester, MN-based Mayo Clinic to halt a seizure in a pig, which had been induced under anesthesia.

"There's a strong proof of concept," says Yizhar, who foresees further advances in his research leading to regulatory approval within the next decade.

In 2022, he co-founded a startup, Modulight.bio, at first based in Israel, and now in Boston, to eventually commercialize the technology as a treatment for neurological conditions, in some cases replacing ineffective medications, and in others providing relief where none exists today. Modulight's partners include Mayo Clinic, among others.

"The primary challenge in treating these disorders stems from a lack of precision therapies that target only the affected neurons and pathways," Modulight.bio states on its website. "Consequently, millions of patients are overtreated with therapies that have broad and often negative effects on brain function. At Modulight.bio, we are pioneering a revolutionary optogenetic therapeutic platform for severe neurological disorders that restores balance to the brain by precisely targeting pathological activity when and where it occurs."

In a similar vein of using precision procedures that minimize damage, Dr. Razansky described his work with both optical and acoustic technologies aimed at developing "more efficient and less intrusive ways to alter and observe brain activity."

Razansky holds dual positions, one as full professor of biomedical imaging at the Faculty of Medicine at the University of Zurich, and the other as full professor at the Department of Information Technologies and Electrical Engineering, ETH Zurich.

In his talk "Combining light and sound for scalable brain interrogation and stimulation," he outlined improvements in methods both for interrogating the brain and for modulating neural activity. For those who talk the talk: he touched on neuroimaging techniques including functional optoacoustic neuro-tomography for whole-brain imaging, localization optoacoustic tomography, large-field multifocal illumination microscopy, and super-resolution fluorescence localization imaging.

Razansky's research has implications in treatment of a range of neurological and neurodegenerative diseases and afflictions including Parkinson's, Alzheimer's and strokes.

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