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Research Highlight

Upconversion nanoparticle mediated optogenetics for targeted deep brain stimulation

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Brain is often called the last frontier in science [1]. It is such an important organ that controls our mind and behavior, yet we know so little about it. The gel-like tissue is probably the most complicated object in the universe because it contains about 100 billion nerve cells, equal to the number of stars in our galaxy, the Milky Way. Each neuron is connected to thousands of other nerve cells by up to 40,000 individual connections called synapses, which forms an exceedingly complex network [1]. This extremely complicated network creates consciousness, processes sensory input, and controls muscles and all other organs. Things can go awry in the brain to induce debilitating diseases such as such as Alzheimer's disease, schizophrenia, autism, epilepsy, and traumatic brain injury. Although we have made enormous strides in understanding the chemical and electrical processes on how the brain works, we lack the necessary tools to investigate and deconvolute the mystery of the brain [1]. This is exactly the goal of Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative in 2013 in the US, with the goal to accelerate the development and application of innovative technologies or tools for researchers to produce a revolutionary dynamic view of the brain that shows how individual cells and complex neural circuits interact in both time and space for the first time [1,2]. Similar programs are now widespread around the world.

One of the biggest challenges of brain research is how to single out the contribution of a specific neuron types to brain functions and brain disorder states in this ultra-complex network [3,4]. Ten years ago, a technique called optogenetics was developed, which combines lasers, fiber optics, and genes for light-responsive protein channels called microbial opsins from algae and bacteria to control neural activity precisely in specific nerve cells within whole living brains as animals carry out their daily activities [3]. Briefly, a natural light-sensitive ion-transporting membrane protein (e.g., channelrhodopsin (ChRs), chloride-conducting ChRs (ChloCs)) is expressed in neurons of choice. Shining light to the cells will open the ion channels to generate electrical signals to either stimulate or inhibit neuronal activities. Since the first demonstration of this approach in cell cultures, optogenetics has become the method of choice in neuroscience, which has been successfully applied in many animal models including Caenorhabditis elegans, Drosophila melanogaster, zebrafish, mice, and nonhuman primates [3,4]. For mammalian models, because of the larger brains that strongly scatter and absorb high energy blue and green lights, insertion of invasive optical fibers is required. Although near infrared laser has been shown to allow deep tissue penetration and induce in vivo stimulation, the depth of this focal excitation is restricted to shallow brain areas because of light scattering. In addition, NIR photons have low energy that is not enough to trigger the light-sensitive ion channels. Thus there is missing link that could connect the NIR to optogenetics to develop noninvasive deep brain stimulation [5].

Chen et al. [5] in *Science* developed transcranial NIR optogenetic stimulation of specifically labeled neurons in deep brain areas, where tissue-penetrating NIR light is locally converted to visible light by upconversion nanoparticles at levels sufficient for activating neurons (Fig. 1). The key component in this method is the use of lanthanide-doped upconversion nanoparticles (UCNPs) that are capable of converting low-energy incident NIR photons into high-energy visible blue or green light that could subsequently activate the light sensitive channels expressed on neuronal cells. UCNPs are synthesized by dispersing trivalent lanthanide ions (e.g., Tm^{3+}, Er^{3+}) in dielectric RE-based lattice [5]. They are capable to absorb multiple low-energy photons sequentially in a ladder-like fashion leading to the production of higher energy anti-Stokes luminescence (Fig. 1). The emission wavelength can to be tuned from NIR, visible, to UV range, depending on the type of lanthanide being used. UCNPs offer advantages over organic fluorophores including high resistance to photobleaching and photochemical degradation, which allows UCNPs to be considered as promising new bio-imaging agents, such as single-molecule tracking, multiplexed labeling, and deep tissue imaging [6]. In this study, the UCNPs were implanted in the ventral tegmental area (VTA) of the mouse brain, a region in deep brain located ~4.2 mm below the skull. Upon transcranial delivery of 980 nm NIR laser pulses, an upconverted emission with a power density exceeds the level that is sufficient for ChR2 activation. The authors successfully demonstrated the application of in vivo upconversion optogenetics to stimulate dopamine release by activating neurons in the VTA,

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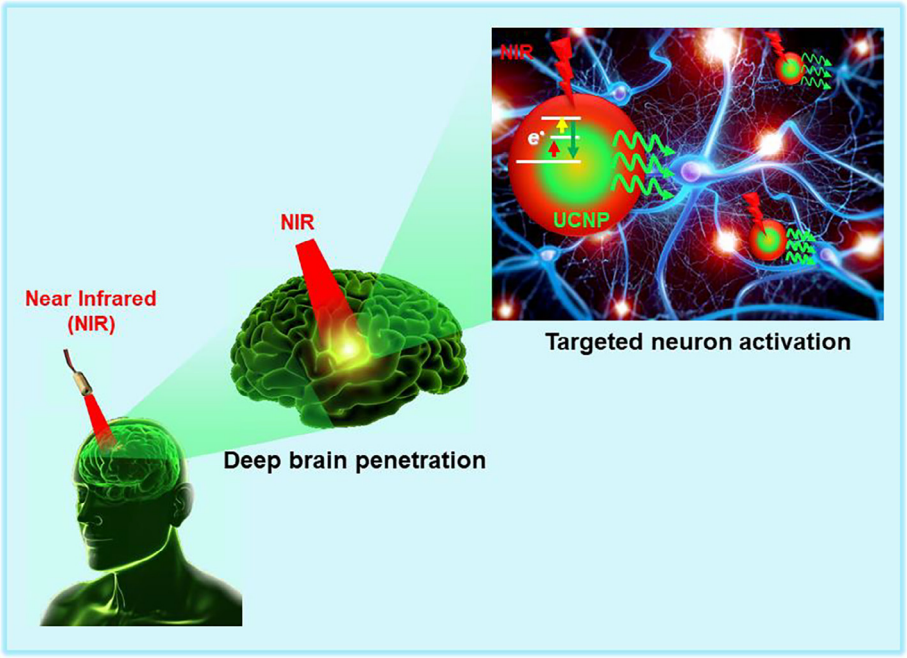


Fig. 1. (Color online) Upconversion nanoparticle mediated optogenetics for targeted deep brain stimulation. Putative noninvasive deep brain stimulation in humans as a potential future development based on the *Science* study. This is achieved by using the near infrared (NIR) that are able to penetrate through the cranial structures into the deep brain as well as the use of upconversion nanoparticles that are able to convert low energy NIR photons to blue or green light that can trigger the opening of light-sensitive ion channels selectively expressed on specific groups of neurons that lead to stimulation or inhibition of brain functions.

inhibit neural activity in the hippocampus, or trigger memory recall by targeting NIR excitation to granule cells in the hippocampus. The in vivo effect of NIR stimulation in this experiment was observed two weeks after the injection of UCNPs and there were no extensive diffusion or degradation of UCNPs one month after injection, suggesting they are stable for relatively long-term in vivo. These findings demonstrate that UCNP-mediated optogenetics is a flexible, robust, and minimally invasive nanotechnology-assisted approach for optical control of in vitro and in vivo neuronal activity. The applicability of this approach lies in the capability to perform spectral tuning of UCNPs that is compatible with the current toolbox of light activated channels that is sufficient for functional activation and inhibition across a variety of deep brain structures. This method, combined with the enhanced ability to selectively express light-sensitive channels in the brain, may allow UCNP-mediated neuronal control to complement or extend current approaches to deep brain stimulation and neurological disorder therapies [5].

Despite the progress, there are some major issues with this technology. First, the method is not truly noninvasive since it still needs injection of viruses carrying genes encoding light-sensitive ion channels and upconversion nanoparticles into the brain [5]. Second, UCNPs has low efficiency of the upconversion, which can only convert around 2 percent of the near-infrared light they received. Thus, the high energy need for the UCNPs could be high, which will limit the choice of portable, miniaturized, and wireless LEDs as the power source [5]. Third, the cells in the brain including neurons and the microglial cells (resident macrophage cells in the brain), may take up the nanoparticles and microglial cells could translocate to other places in the brain, and the influence of cellular uptake and migration may affect the long term in vivo effects [6,7]. In addition, recent findings show that rare earth based UCNP could undergo degradation and transformation in the acidic lysosomal compartment after phagocytosis by macrophages. On the one hand, dissolved rare earth ions have high binding affinity to phosphate groups, and lysosomal membrane is a major source of phospholipids [6,7]. The binding and stripping of rare earth phosphate groups from the membrane would lead to lysosomal membrane damage, release of cathepsin B, which activates NLRP3 inflammasome to produce IL-1β, which is a major pro-inflammatory cytokine. It is possible that this process could happen in microglial cells that have taken up the UCNPs, which has the potential to induce focal inflammation in the brain tissue. On the other hand, transformation of UCNPs will lead to compromise or loss of upconverting capability of the nanoparticles, which will reduce or lose the effectiveness of deep brain stimulation in this optogenetics model [6].

Despite these shortcomings, upconversion optogenetics make it possible for the first time to conduct therapeutic deep-brain stimulation in a relatively noninvasive way [5]. The traditional deep brain stimulation method uses a pacemaker-like device that connects to electrode inserted in the brain to treat diseases including Parkinson's and epilepsy. The technique along with the traditional optogenetics, are quite invasive because the fiber optics and electrodes are needed to be surgically implanted in the brain [4]. Obviously, the upconversion optogenetics method could be further improved by developing methods for genes and UCNP delivery that could cross the blood brain barrier and gain access to the targeted areas of the brain. Moreover, the upconverting efficiency needs to be improved to decrease the energy demand. The long term stability and safety of the UCNPs in brain in vivo also needs to be considered [8–10]. In addition, the demonstration of this technique in mice as the animal model is not enough, larger animals including the non-human primates are needed to prove its efficacy before clinical trials. In summary, the study is the first step in developing a truly noninvasive therapeutic method to treat brain diseases.

Conflict of interest

The author declares that he has no conflict of interest.

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References

[1] Insel TR, Landis SC, Collins FS. The NIH BRAIN initiative. Science 2013;340:687–8.
[2] Weiss PS. President Obama announces the BRAIN initiative. ACS Nano 2013;7:2873–4.
[3] Boyden ES, Zhang F, Bamberg E, et al. Millisecond-timescale, genetically targeted optical control of neural activity. Nat Neurosci 2005;8:1263–8.
[4] Deisseroth K. Optogenetics: 10 years of microbial opsins in neuroscience. Nat Neurosci 2015;18:1213–25.
[5] Chen S, Weitemier AZ, Zeng X, et al. Near-infrared deep brain stimulation via upconversion nanoparticle-mediated optogenetics. Science 2018;359:679–84.
[6] Li RB, Ji ZX, Dong JY, et al. Enhancing the imaging and biosafety of upconversion nanoparticles through phosphonate coating. ACS Nano 2015;9:3293–306.
[7] Li RB, Ji ZX, Chang CH, et al. Surface interactions with compartmentalized cellular phosphates explain rare earth oxide nanoparticle hazard and provide opportunities for safer design. ACS Nano 2014;8:1771–83.
[8] Mirshafiee V, Jiang W, Sun BB, et al. Facilitating translational nanomedicine via predictive safety assessment. Mol Ther 2017;25:1522–30.
[9] Nel A, Xia T, Madler L, et al. Toxic potential of materials at the nanolevel. Science 2006;311:622–7.
[10] Nel AE, Madler L, Velegol D, et al. Understanding biophysicochemical interactions at the nano-bio interface. Nat Mater 2009;8:543–57.



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