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Development of Wireless Opto-Neural Probe with Upconversion Nanoparticles (UCNP) for Optogenetics

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Abstract

In order to reduce the invasiveness to the brain and the activity limitation of experimental animals, a neural probe with a wireless optical stimulation function is required. In this study, we realized a completely wireless opto-neural probe using upconversion nanoparticles, which enable optical stimulation with NIR irradiation from outside the body. We successfully fabricated several kinds of opto-neural probes with different UCNP, and succeeded in emitting different lights. We obtained sufficient light emission intensities to optically stimulate the light-sensitive protein.

1. Introduction

Optogenetics has recently attracted much attention in neuroscience. Optogenetics can control activities of neurons with optical stimulation by expressing light-sensitive proteins such as a channelrhodopsin-2 (ChR2) and an archaerhodopsin-3, in the cell membrane of the neuron. It is possible to perform both excitation and inhibition of cells by using different light-sensitive proteins. Therefore, optogenetics can be considered as one of the most effective methods to investigate brain functions. In general, optical fibers, optical waveguides, and LEDs embedded in neural probes are usually used to optically stimulate brain tissues [1]-[3]. However, these neural probes need optical or electrical wires for the interconnection between the neural probe and the external devices. Fig. 1(a) shows optical stimulation of nerve cells by a conventional neural probe. Wired connections may induce severe damages to the brain and suppress animal activity [4]. Therefore, wireless opto-neural probes which can suppress invasiveness and activity limitation are strongly required.

2. Opto-neural probe with UCNP

Recently, upconversion nanoparticles (UCNP) which can perform upconversion light emission following a multi-step energy transfer process have developed. UCNP can emit visible light by absorbing near-infrared (NIR) light. The absorption and emission wavelengths can be controlled by adjusting both kinds and ratios of the elements in the UCNP. We can wirelessly stimulate nerve cells expressing light-sensitive proteins using an opto-neural probe with UCNP, as shown in Fig. 1(b). This opto-neural prove with UCNP can emit visible light to neurons by NIR light irradiation from outside the body. Therefore, thanks to UCNP, we can realize a wireless opto-neural probe, leading lower invasiveness and enabling animals to move freely during experiments.

3. Fabrication of the opto-neural probe with UCNP

We fabricated the opto-neural probe using photo-sensitive resin, SU-8, mixed with UCNP. As the UCNP used in this study consists of ytterbium (Yb) and erbium (Er) and has a particle size of 2 -10 μm, it has an excitation wavelength of 980 nm and an emission peak wavelength of 450 nm (blue) or 540 nm (green). Fig. 2 shows green and blue light emissions from the UCNP used in the experiment. In addition, as SU-8 has higher flexibility compared with Si, the SU-8 based opto-neural probe can reduce the damages to brain cells. Fig. 3 shows the process flow of the opto-neural probes with UCNP. First, we deposited SiO_2 on 2-inch Si wafer by plasma-enhanced chemical vapor deposition (PE-CVD). Then, upconversion emission parts were formed by patterning of SU-8 including UCNP. Here, concentrations of UCNP were 2.25, 4.5, 10, and 20vol%. Next, SU-8 was patterned in the form of the probe. The width and length of the probe shank were 200 μm and 10 mm, respectively. The upconversion emission parts composed of SU-8 and UCNP were fabricated at 1 mm from the probe tips. Finally, opto-neural probes with UCNP were released from the Si wafer by dipping in an aqueous hydrofluoric acid solution. Fig. 4 shows the photographs of the fabricated opto-neural probes with UCNP. We conformed the upconversion light emission from UCNP with NIR irradiation.

4. Experimental results and discussion

In this study, we investigated the characteristics of the opto-neural probe with blue-light UCNP which can stimulate ChR2. First, we investigated emission intensity characteristics. Fig. 5 shows relationships between the UCNP concentration and blue light emission intensity for different SU-8 thicknesses. The light emission intensity increases with an increase of the UCNP concentration. Fig. 6 shows relationships between the SU-8 thickness and blue light emission intensity for different UCNP concentrations. A threshold power density to activate neurons expressing ChR2 is approximately 1 mW/mm^2. In the case of the concentration of 2.25vol%, the emission intensity didn't achieve the threshold value. In contrast, in the case of the concentration of 4.5vol%, the emission intensities were larger than the threshold value for different SU-8 thicknesses.

The photograph of the in-vivo experiment with the fabricated opto-neural probe with UCNP is shown in Fig. 7. We observed that mouse moved with NIR irradiation. Table 1 summarized the light stimulation methods for optogenetics.

5. Conclusions

In this study, we proposed and fabricated wireless opto-neural probes with UCNP for optogenetics. The opto-neural probes successfully emitted visible lights by the multi-step energy transfer process with NIR irradiation. The probe can achieve lower invasiveness and make animals to move freely during experiments. The opto-neural probe with UCNP can be considered as one of the most valuable tools for optogenetics and neurophysiology.

References

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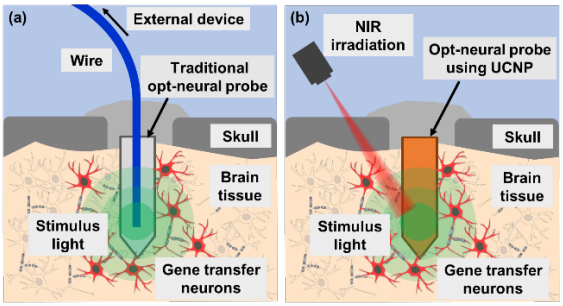

Fig. 1. Schematic illustrations of optical stimulation by opto-neural probe.
(a) conventional (wired) and (b) proposal (wireless).

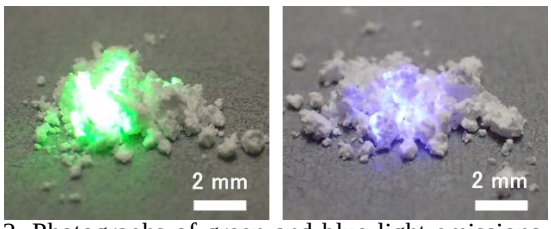

Fig. 2. Photographs of green and blue light emissions from different UCNP with NIR irradiation.

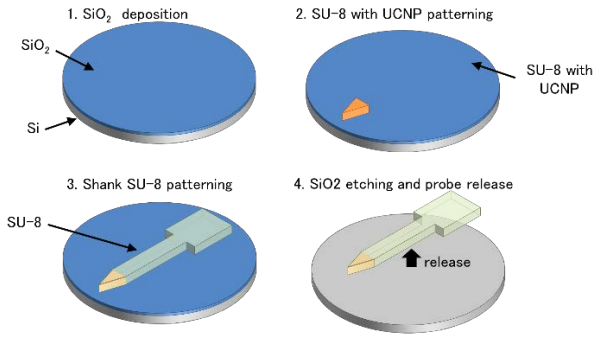

Fig. 3. Process flow of the opto-neural probe with UCNP.

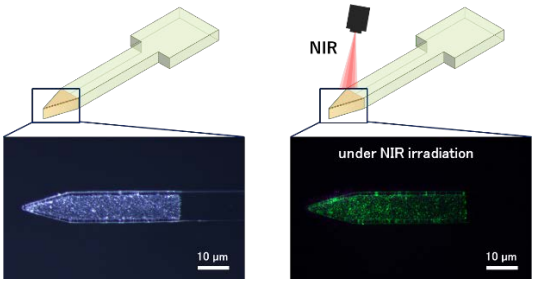

Fig. 4. Photographs of the opto-neural probe with and without NIR irradiation. Green light was emitted with NIR irradiation.

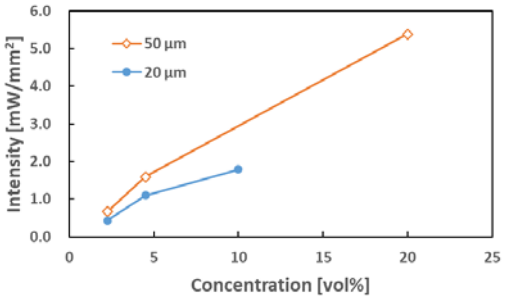

Fig. 5. Relationships between the UCNP concentration and blue light emission intensity for different SU-8 thicknesses.

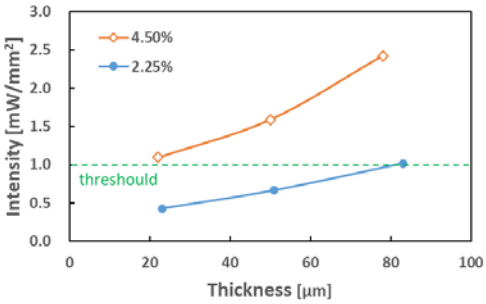

Fig. 6. Relationships between the SU-8 thickness and blue light emission intensity for different UCNP concentrations.

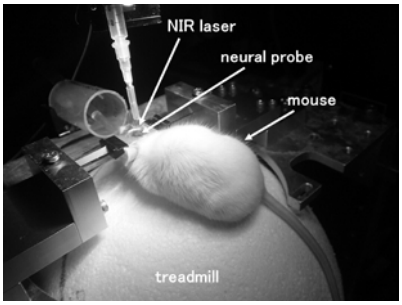

Fig. 7. Photograph of in-vivo experiment.

Table 1. Summary of the light stimulation methods for optogenetics.

Method	Optical fiber	Optical waveguide	LED	UCNP
Interconnect	Optical fiber	Optical fiber	Electrical wire	None
Heat generation	No	No	Yes	No
External light source	Necessary	Necessary	Unnecessary	Necessary