Implantable imaging devices for biomedical applications

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ABSTRACT
This paper describes an in vivo implantable ultra-compact CMOS imaging device and its biomedical applications. First, I introduce Photoceuticals, a new concept for diagnosis and treatment using optoelectronics technology. Next, I present the method of measuring neural activity in the brain by fluorescence and outline the ultra-compact CMOS imaging device developed for implantation in the mouse brain. Taking advantage of the device’s small size and lightweight, the devices have simultaneously been implanted in two different mouse brain regions. The results of applying the device to painful phenomena with complex mechanisms are described. Finally, conclusions and future prospects are presented.

1 Introduction
Our bodies have various nervous systems that facilitate intercommunication through electrical signals. As a result, it has become possible to measure and regulate the functions of the nervous system in the body by electrical means, which has been widely employed in medical devices for diagnosing and treating diseases. Recently, there has been a growing interest in Electroceuticals, in which small devices that perform electrical stimulation and electrical measurements are implanted in the body to diagnose and treat affected areas locally.

In contrast to electricity, light has little effect on living organisms; light-receiving functions, for example, are found only in specialized cells such as photoreceptor cells. However, advances in genetic engineering have made it possible to measure and modulate certain neural functions, such as the dopaminergic nervous system, with light. I have proposed the concept of Photoceuticals, which, like Electroceuticals, is a new approach that uses precise measurement and control of biological functions with light to diagnose and treat diseases [1].

Usually, pharmaceuticals exert non-local effects and can cause nonspecific side effects because they act on areas beyond the disease site after administration. In contrast, electroceuticals are implanted near the affected area and produce local effects but may stimulate all nearby nervous systems, resulting in nonspecific effects. In contrast, photoceuticals can accurately measure and control the activity of specific nervous systems localized only in the vicinity of the implantation site. This innovation holds promise as a therapeutic approach for historically challenging diseases such as pain and epilepsy. Figure 1 compares pharmaceuticals, electroceuticals, and photoceuticals. Regarding local and specific effects on biological functions, photoceuticals are expected to have superior efficacy in diagnosis and treatment.

The development of ultra-compact optoelectronic devices is necessary for the realization of photoceuticals. In this talk, I will describe the basic characteristics and applications of these devices, mainly focusing on in vivo implantable CMOS imaging devices.

2 Overview of ultra-compact CMOS imaging devices implanted in the brain

The GCaMP is a protein that detects calcium ions and emits GFP (Green Fluorescent Protein). Since neuronal activity is closely related to calcium ions, the intensity of fluorescence can be measured to determine neuronal activity. Fluorescence microscopy is widely used to measure fluorescence, but it is challenging to measure neuronal activity in the mouse brain under free-running conditions. Therefore, the methods shown in Figure 2 have been proposed [2].

Fig. 2 Classifications of fluorescence detecting devices implanted in mouse brain [2]. (a) Fiber photometry. (b) Head-mounted optical microscope device. (c) Implantable micro imaging device.

The first method (Figure 2(a)) is called fiber photometry, in which an optical fiber is inserted into the brain to measure fluorescence [3]. The second method
(Figure 2(b)) is a small microscope system mounted on a mouse head [4]. A rod lens inserted into the brain acquires fluorescent images, and the images are observed by a small microscope system mounted on the head of a mouse. I have proposed a third method (Figure 2(c)) in which a device equipped with an ultra-small LED for fluorescence excitation and a CMOS image sensor for fluorescence measurement is directly inserted into the mouse brain.

Fiber photometry (Figure 2(a)) has been widely used recently because of its simplicity. Optical fibers are susceptible to bending, which can somewhat interfere with the free behavior of the mouse. In addition, imaging cannot be performed only by changing the light intensity. There is a report that imaging is possible by using bundle fibers, but the rigidity of the fibers becomes higher, and free movement becomes more difficult. In contrast to fiber photometry, the small head-mounted microscope shown in Figure 2(b) is capable of imaging. On the other hand, the head-mounted module weighs more than 2 g, which is about 10% of a standard mouse's body weight, placing a heavy burden on the mouse. In addition, the invasiveness of rod-lens puncture is also an issue, depending on the puncture site. On the other hand, the ultra-compact imaging device shown in Figure 2(c) is small and lightweight, and thus less invasive and does not interfere with the free behavior of mice [2]. It also allows observation over a wide area. However, the spatial resolution is lower than that of the head-mounted microscope because it is a contact-type imaging device without any optical system such as a lens. Another advantage of this method is that multiple devices can be simultaneously inserted into the mouse brain because of its small size and lightweight. This makes it possible to measure neural network activity in multiple brain regions, which is helpful for elucidating complex neural networks in the brain. The CMOS image sensor is fabricated using semiconductor integrated circuit technology, which enables multimodal measurement by integration with other functions, such as extracellular potential measurement, and is expected to help analyze various aspects of neural activity.

3 Application of an ultra-compact brain-implanted CMOS imaging device to pain phenomena

Pain is a natural defense response essential to avoid potential tissue damage or injury. However, when pain persists for long periods, it can shift from acute pain to chronic pain, which is clinically and economically burdensome. Chronic pain is one of the leading causes of disability and requires treatment.

This pain is sensed by nociceptors and transmitted through complex processing in the central nervous system (CNS). To date, understanding the principles and mechanisms governing neural coupling in the encoding and decoding of pain signals remains one of the significant challenges in pain research. Given the importance of multiple brain regions in regulating and controlling pain, simultaneous observation of brain activity in various locations is necessary to elucidate this phenomenon.

![Fig. 3 Implantable microimaging device. (a) Device photos and specifications. (b) Device fabrication process [5].](image)

The surface of the CMOS image sensor mounted on the ultra-compact imaging device has an optical filter that suppresses excitation light and allows fluorescence to pass through. The entire surface of the device is coated with transparent Parylene C, which is biocompatible and waterproof. Figure 3(a) shows an overview of the ultra-compact implantable CMOS imaging device that can be implanted in the mouse brain [5]. Figure 3(b) shows a fabrication process of the device [5]. Since the device targets GCaMP measurement, it has an LED with a central emission wavelength of 473 nm.

![Fig. 4 The experimental setup of pain by using two micro-imaging devices [6].](image)
implanted in a mouse's dorsal raphe nucleus (DRN) and central amygdala (CeLC) [6]. Both areas are involved in pain phenomena. Pain is induced by injecting formalin into the mouse foot. As shown in Figure 4, a system was constructed to simultaneously monitor fluorescence measurement and mouse behavior. The experimental results clearly demonstrated changes in fluorescence intensity and foot-licking behavior (licking) related to pain in these two regions [6]. As a control, PBS was injected instead of formalin. It can be seen that different responses were observed in the two regions in response to the formalin injection. A significant feature is the ability to implant and measure two devices in different brain regions simultaneously. It may be helpful in elucidating phenomena that span multiple brain regions, such as pain.

4 Conclusions and Future Perspectives

I introduced an ultra-compact CMOS imaging device that can be implanted in the mouse brain and described its basic structure and application to measure pain phenomena. The device helps measure complex brain network phenomena by measuring multiple regions. This miniature CMOS imaging device can be used as a diagnostic device in photoceuticals. Further optical stimulation devices are needed to realize future photoceuticals. My research group also reported a photo-stimulation device using an ultra-compact LED array. The device was implanted in the mouse brain's ventral tegmental area (VTA), where dopamine neurons are abundant, and successfully detected dopamine release by photo-stimulation [7]. The combination of this light-stimulation device and an imaging device is expected to realize photoceuticals.

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References