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Review Article

Optogenetic exploration and modulation of pain processing

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ABSTRACT

Intractable pain is the single most common cause of disability, affecting more than 20% of the population worldwide. There is accordingly a global effort to decipher how changes in nociceptive processing in the peripheral and central nervous systems contribute to the onset and maintenance of chronic pain. The past several years have brought rapid progress in the adaptation of optogenetic approaches to study and manipulate the activity of sensory afferents and spinal cord neurons in freely behaving animals, and to investigate cortical processing and modulation of pain responses. This review discusses methodological advances that underlie this recent progress, and discusses practical considerations for the optogenetic modulation of nociceptive sensory processing.

1. Introduction

Pain is a complex sensory and emotional experience that involves a highly regulated interplay between the peripheral nervous system, spinal cord, and brain. The complete pain experience includes sensory-discriminative, affective-motivational and cognitive-evaluative dimensions, and can be modulated at multiple levels of the central nervous system (CNS) (Turk et al., 2010; Quintero, 2013). Pain serves a necessary protective role. The functionally 'normal' pain response induced by actual or threatened tissue damage is essential for the protection of an individual against harmful external noxious influences. Normally, pain is restricted to the site of injury and resolves after healing. This short-lasting pain is described as "acute". However, chronic pain can persist long after the initial injury is healed and can occur even in the absence of any obvious trigger. Chronic neuropathic pain can arise from damage to or disease of the somatosensory nervous system. Chronic pain may also arise from altered nociceptive function even in the absence of clear inury or dysfunction ("nociplastic" pain). Neuropathic and nociplastic pain do not serve a protective function and are considered "pathological".

Chronic pain manifests as exaggerated or inappropriate pain sensation of both noxious and innocuous stimulation (hyperalgesia and allodynia). Although a variety of therapeutic strategies to address chronic pain have been developed, the current primary approaches to chronic pain treatment largely fail to address the underlying causes of pathological pain. Indeed, there is a lack of specific and effective treatment for chronic pain and many front-line treatments, such as the antiepileptic drugs or tricyclic antidepressants, have been repurposed for pain treatment. Moreover, current pain therapies such as opioids can have deleterious side effects, such as dependence and addiction (Li et al., 2015 and Pessoa et al., 2015). This lack of effective and specific pain treatments has encouraged the development of continuously more sophisticated technologies and approaches to understand pain physiology and pharmacology with the hope of identifying new targets and methods for treating chronic pain. As described here, the development and adoption of optogenetic approaches for the study of pain has ushered in a new era of cell-specific pain research and modulation that enables the functional interrogation and control of pain processing at unprecedented levels of specificity, both *in vivo* and *in vitro*.

2. Opsins and optogenetics

Optogenetics is a powerful approach that works by introducing photo-excitable proteins, opsins, into physiologically or genetically defined neural populations. These opsins typically allow the use of light to either directly excite or inhibit neurons, or to allow light-activated modulation of subcellular functions. Most commonly used opsins in neuroscience research are proteins that enable the light-activated flux of ions across the cell membrane. Opsins can possess differing spectral sensitivity, mechanism of function, and net effect on the cell. For instance, channelrhodopsin is a cation channel that is activated by blue light and results in cell depolarization. On the other hand, halorhodopsin is an anion pump that is activated by yellow light and produces cell hyperpolarization (see review (Zhang et al., 2011), and Table 1 for information about the most commonly used opsins). Of critical importance to these advances, the implementation of light as activator

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Table 1
Characteristics of opsins mostly used in neuroscience.

Opsins	Wavelength	Nature	Effects on cells
ChR2, ChIEF, ChR1/2 chimeras, ChETA	470 nm	Proton channel	Depolarization
VChR1	535 nm	Proton channel	Depolarization
NpHR	589 nm	Chloride channel	Hyperpolarization
Arch	550 nm	Proton	Hyperpolarization

enables a very tight control over the time which specific neuronal populations can be activated. Thus, light-activated opsins have enabled the use of light to control neural activity with unprecedented temporal precision.

3. Application of optogenetics in pain modulation at different levels of nervous system

Since the introduction of optogenetics into neuroscience, several pain studies utilized this novel approach at different levels of the nervous system in order to elucidate the mechanisms of pain modulation (Table 2). It is notable, however, that optogenetic modulation of sensory processing at the peripheral and spinal levels has lagged behind similar milestones in the control of brain function. This lag is due in part to the inherent difficulties in the precise delivery of light to the spinal cord and periphery to activate opsins. One of the first demonstrations of optogenetic modulation of pain used an animal model where channelrhodopsin was expressed in $Na_v1.8$-expressing nociceptors (Daou et al., 2013). In this model, it was possible to provide light from an external light source to induce nocifensive responses in the mice. Yet, this approach to sensory optogenetics has considerable limitations for the study of freely behaving animals, which might avoid light stimuli when such light activates nociceptors. Thus, several approaches (Fig. 1) have been recently developed to deliver light to freely behaving animals, including the incorporation of an illuminated cuff around key nerves of interest (Towne et al., 2013), wireless delivery of light to the spinal cord and afferent terminals (Montgomery et al., 2015), and epidural optogenetic fibers (Bonin et al, 2016). The use of these latter approaches to study pain processing in freely behaving animals allows a unique, functional investigation of the complex circuitry that modulates pain behaviour, including intrinsic spinal neurons and descending modulatory signals from the brain to spinal cord.

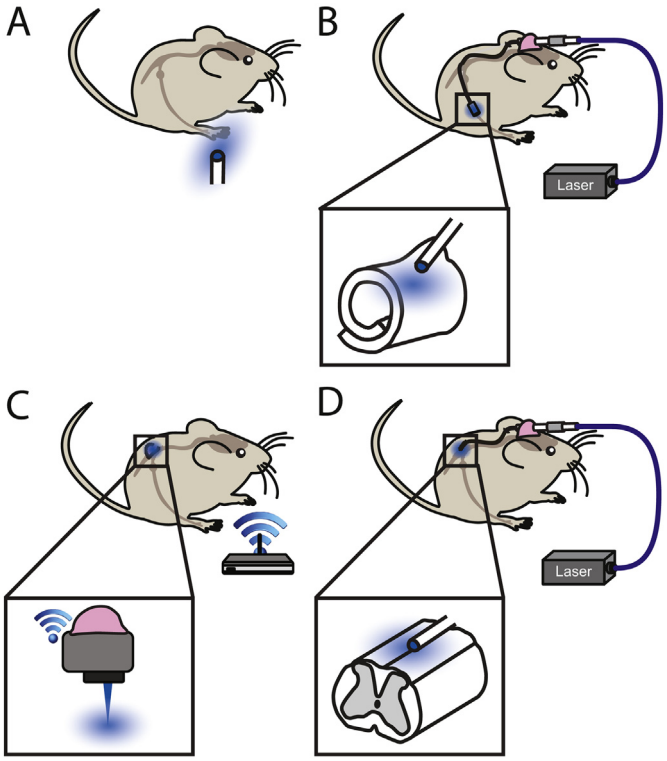

Fig. 1. Novel approaches for light delivery in sensory optogenetics. A) Early studies on sensory optogenetics used peripheral light to directly modulate sensory neurons expressing opsins. Further development restricted the delivery of light to neurons of interest, including (B) an illuminated cuff to deliver light to the sciatic nerve (Towne et al., 2013), (C) the wireless delivery of light to the dorsal horn (Montgomery et al., 2015), and (D) epidurally-implanted optic fibers that can activate both sensory neuron terminals and intrinsic neurons of the spinal dorsal horn (Bonin et al., 2016).

3.1. Peripheral afferents and neurons

The perception of pain begins with the processing of noxious stimuli by primary nociceptors expressed in sensory nerve fibers. Nociceptive information is then transmitted *via* primary sensory neurons to the dorsal root ganglion (DRG) and the dorsal horn of the spinal cord. The signal is then transmitted to higher levels including the brainstem, subcortical structures and the cortex where pain perception occurs.

Table 2
Summary of engineered opsins in study of pain.

Opsins	Targeting cells or tissues	Outcomes	Ref
opto-β2AR	HEK293 cell, BLA	Anxiety-like behavior	Siuda et al. (2015b)
ChR2	Keratinocytes	Activation of sensory neurons	Baumbauer et al. (2015)
VGluT3-ChR2	Hind paw in oxaliplatin pain not CCI pain model	Pain behavior	Draxler et al. (2014)
ChR2-eYFP	Spinal dorsal and DRG $NaV1.8^+$ sensory neuron	Nociceptive behavior	Daou et al. (2013)
ChR2	Spinal dorsal horn PV(+) GABA interneuron	GABA release	Yang et al. (2015)
Arch, ChR2	Spinal GABAergic interneurons, nociceptive afferents	Induction of mechanical hypersensitivity, analgesia	Bonin et al. (2016)
TRPV1-ArchT-eGFP	DRG neuron and periphery	Antinociception	Li et al. (2015); Boada et al. (2014)
ChR2	RVM serotonergic neurons	Persistent pain	Cai et al. (2014)
Opto-MOR	RMT/VTA GABA neuron	Place preference/aversion	Siuda et al. (2015a)
ChR2	Locus ceruleus neuron	Nocicpeiton/antinociception	Hickey et al. (2014)
ChR2-YFP	Parabrachial nucleus and amygdala CGRP neurons	Defensive behavior, threat memory	Han et al. (2015)
ChR2-YFP	Central amygdala	Visceral pain	Crock et al. (2012)
ChR2-eYFP/eNpHR3.0	ACC PV and SOM neurons	Reversal of inflammatory pain	Kang et al. (2015)
ChR2	ACC inhibitory neuron	Pain inhibition	Gu et al. (2015)
ChR2	ACC astrocytes	Sleep disturbance under neuropathic pain	Yamashita et al. (2014)
ArchT	PFC, paraventricular thalamus	Inhibition of visceral pain	Jurik et al. (2015)
ChR2, NpHR3.0	PL-PFC excitatory neurons	Inflammatory pain, anxiety	Wang et al. (2015)
ChR2-eYFP	PFC	Antinociception	Lee et al. (2015)