Journal of Pain Research

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REVIEW

Looking for a Beam of Light to Heal Chronic Pain

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Abstract: Chronic pain (CP) is a leading cause of disability and a potential factor that affects biological processes, family relationships, and self-esteem of patients. However, the need for treatment of CP is presently unmet. Current methods of pain management involve the use of drugs, but there are different degrees of concerning side effects. At present, the potential mechanisms underlying CP are not completely clear. As research progresses and novel therapeutic approaches are developed, the shortcomings of current pain treatment methods may be overcome. In this review, we discuss the retinal photoreceptors and brain regions associated with photoanalgesia, as well as the targets involved in photoanalgesia, shedding light on its potential underlying mechanisms. Our aim is to provide a foundation to understand the mechanisms underlying CP and develop light as a novel analgesic treatment has its biological regulation principle for CP. This approach may provide an opportunity to drive the field towards future translational, clinical studies and support pain drug development.

Keywords: chronic pain, light therapy, photoanalgesia, brain regions, molecular targets

Introduction

The eyes are important visual organs. The eyes can perceive light and convert stimuli to electrical signals. Besides their function in imaging, they also have many nonimaging functions, participating in processes such as the circadian rhythm, sleep quality, mood, and learning.[1–3] Recent studies also found that optical signals play an analgesic role.[4–7] Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage.[8] It can be categorized as nociceptive (from tissue injury), neuropathic (from nerve injury), or nociplastic (from a sensitive nervous system).[9] Chronic pain (CP) is defined by the International Association for the Study of Pain as "persistent or recurrent pain lasting longer than 3 months".[10] Chronic pain is a very common disorder with an estimated global prevalence of about 20%.[11] The Global Burden of Disease Study 2019 revealed that CP was the greatest cause of years lived with disability worldwide.[12,13]

At present, treatment of CP is not efficient, causes side effects, and may lead to drug tolerance,[14] which results in poor treatment outcomes and a heavy burden on patients.[9,15] Although various nonpharmacological treatment methods are available, including surgery, regional anesthesia, neuromodulation, and rehabilitation programs, pain is not reduced to a sufficient degree in many CP patients. Generally speaking, pain is rarely completely eliminated, and highly effective treatment methods are still lacking.[16] There is an urgent need to improve the pain treatment approaches without inducing adverse side effects.

Light therapy has several advantages; it is noninvasive, convenient, and cost-effective. Exposure to light of specific wavelengths and intensities has shown to be effective in the management of various health conditions, such as cancers,[17] skin diseases,[18] sleep disorders,[19] and affective disorder.[20] Recently, light therapy has been used for various pain conditions, including chronic nonspecific low back pain,[21] fibromyalgia pain,[22] migraine headaches,[6] and neuropathic pain.[23] Based on this technique, optogenetic techniques have been developed that enable the control of cellular activity through ectopic expression of light-activated optogenetic proteins in genetically modified target cells.[24,25]

Received: 18 December 2023
Accepted: 5 March 2024
Published: 16 March 2024

In this review, we discuss how light can be used to induce analgesia, including the retinal photoreceptors involved in photoanalgesia and the brain regions associated with these photoreceptors. We also discuss the mechanisms underlying the analgesic effects of light in CP, as well as the principle and application of some derivative technologies in which light plays a therapeutic role. We strive to adequately expound how light serves an analgesic function through the visual pathway and the biological mechanisms through which light acts on pain, as well as the current applications of phototherapy to relieve pain. We hope this review helps to generate new scientific hypotheses, probe physiological mechanisms, develop therapeutic strategies, reveal the value of photoanalgesia techniques, and promote the fundamental research, clinical treatment, and drug development in the area of CP.

Characteristics of Light Exerting Analgesic Effects in CP

Alteration of the intensity of light in the environment impacts several physiological functions. The light environment plays a crucial role in the circadian rhythm, sleep quality, mood, and learning, which are essential for our health and quality of life.[1–3] Furthermore, an increasing body of evidence suggests that bright light has an antinociceptive effect in various pain conditions. In the clinic, increased sunlight exposure decreases pain in patients after spinal surgery,[26] and bright light appears to improve the symptoms of patients with headache,[27] fibromyalgia,[28] and chronic low back pain.[29,30] A recent study evaluated the effects of exposure to light of various intensities (0, 200, 1000, 3000, and 5000 lux) in wild-type animals through nocifensive behavior tests; it was found that an intensity greater than 3000 lux was required to significantly upregulate the pain threshold.[31] Another study found that migraine patients have different pain indices in different seasons; the pain index is reduced in seasons of higher light intensity.[32] Similar findings were observed in mice whose cold pain and mechanical pain thresholds changed when they were placed in a dim light environment.[33] In addition, two proof of concept studies, one in women with fibromyalgia[28] and the other in military veterans with chronic low back pain,[29] showed that sitting in broad-spectrum bright white light (>3000 lux) for 1 h per day upon waking in the morning improved pain sensitivity and behavior. All the abovementioned bright light treatments lasted for several hours before analgesic effects were observed. On the contrary, various studies have confirmed that short-term intense light therapy has no analgesic effects, but aggravates pain.[34,35] In summary, these results indicate that exposure to high-intensity light for several hours can relieve the sensation of pain.

Beside of intensity, various experiments focused on the therapeutic effect of light wavelength on pain (Table 1). The wavelength of light determines the visual color presentation of our eyes, although the range of the visible spectrum to the human is limited. Recently, short wavelength laser/light therapy has been used for the management of various pain conditions. It may contribute to the photopigment found in retinal ganglion cell is melanopsin and has a peak spectral sensitivity of 480nm, which falls in the blue/cyan range of visible light. It's understandable that a study reported that red light administered through visual pathways caused thermal hyperalgesia and mechanical allodynia in rats.[36] Consistent with the characteristics of melanopsin, most studies have reported the beneficial effects of green/blue light.[37,38] For instance, exposure to green light via the visual system resulted in lesser pain in an acute migraine episode compared to the exposure of other wavelengths such as white, blue, amber, and red.[39] And Tang et al[5] unilateral intra-articular injection of complete Freund's adjuvant in mice to produced mouse model of arthritic pain, then exposed the models to green light. After six consecutive days with 8 hours daily exposure, hyperalgesia of models had significant relief. Consistently, there is a study have reported that exposing in green light produced long-lasting antinociceptive effects in rats, in the same condition opaque contact lenses prevented antinociception.[40] And rats fitted with green contact lenses exposed to room light exhibited antinociception arguing for a crucial role of the visual system. In addition, clinical studies have shown that green light is effective for headache relief.[6]

Retinal Photoreceptors That are Involved in Photoanalgesia

The mammalian eye contains three classes of photoreceptors with distinct peak excitation wavelengths and photo-response characteristics: rods and cones ("canonical" photoreceptors) in the outer retina[44] and melanopsin-expressing intrinsically photosensitive retinal ganglion cells (ipRGCs; "noncanonical" photoreceptors) in the inner retina[45] (Figure 1). Cones and rods, which work together to capture visual information and respond to light, are considered as the origin of the visual pathway in the retina.[44,46] They show different light sensitivities; in bright environments, our vision is almost completely mediated by the cones, which are not very light-sensitive and provide vision in bright light, yet the proportion of cones is barely 5% (4.6 million out of 92 million) of our retinal photoreceptors. In contrast to rods,

Table 1 Summary of Studies on the Effects of Different Light Wavelengths on Pain Through Visual Pathways

Color/Wavelength	Exposure	Intensity/Irradiance	Pain Condition	Δ Pain	Ref
White 390–740nm	9 min	9.1×10^3μW/cm^2	–	↑	[34]
	6 hr	5000 lux	Chronic nonspecific back pain	↓	[41]
	30 sec	18,000 lux	Fibromyalgia	↑	[39]
	3 min	1–100 cd/m^2	Migraine	↑	[35]
	1 hr	3000+ lux	Fibromyalgia	↓	[28]
	3 min	1–100 cd/m^2	Migraine	↑	[40]
	1 hr	3000+ lux	Chronic low back pain	↓	[29]
	1 hr	3000+ lux	Chronic low back pain	↓	[42]
	10 hr	5 lux	–	↑	[33]
	3 hr	3000 lux	Chronic constriction injury and inflammatory pain	↓	[31]
Blue 450–500nm	3 min	1–100 cd/m^2	Migraine	↑	[39]
	3 min	1–100 cd/m^2	Migraine	↑	[42]
	8 hr	4–5 lux	Functional pain syndromes	↓	[40]
Green 500–565nm	3 min	1–100 cd/m^2	Migraine	↓	[39]
	8 hr	4 lux	Chronic pain	↓	[40]
	8 hr	4 lux	Chronic pain	↓	[36]
	8 hr	10 lux	Inflammatory pain	↓	[5]
Amber 590nm	1–2 hr	4–100 lux	Migraine	↓	[6]
	1–2 hr	4–100 lux	Fibromyalgia	↓	[43]
Red 625–740nm	3 min	1–100 cd/m^2	Migraine	↑	[39]
	3 min	1–100 cd/m^2	Migraine	↑	[42]
	3 min	1–100 cd/m^2	Migraine	↑	[39]
	3 min	1–100 cd/m^2	Migraine	↑	[42]
	8 hr	50 lux	Functional pain syndromes	↑	[36]

cones can perceive different colors.[44] There are three types of cones, namely blue-, green-, and red-sensitive cones, while there is only one type of rod, which is green-sensitive.[47] Rods, which account for 95% of our retinal photoreceptors, are very light-sensitive; they can detect single photons and contribute to human vision only under low light conditions, for example during twilight.[44,47] As the "noncanonical" photoreceptors, ipRGCs capture light by using G protein–coupled receptors (GPCRs) known as melanopsin. The main physiological functions of ipRGC are nonimaging functions, including photic regulation of the circadian rhythm and the pupillary light response.[46]

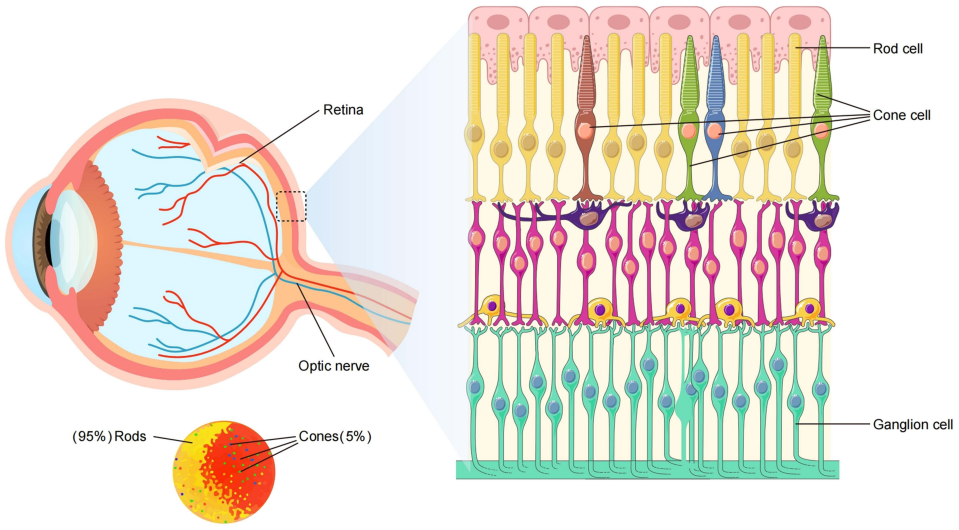

Figure 1 Illustration of retinal photoreceptors.

Rods/Cones

Photophobia, also termed photo-oculodynia, is defined as an abnormal sensitivity to light. People with photophobia usually consider innocuous visual stimuli as noxious or uncomfortable Photophobia may be caused by a variety of ocular diseases.[46] Photophobia is a typical symptom of migraine and has been identified as the most disabling symptom of migraine.[27,48] Based on the physical functions of rods and cones, photophobic migraine causes serious difficulties. Given that migraine has also been associated with abnormal color vision and color discrimination,[49] maladaptive dysfunction of cones and/or rods could play an additional role in migraine photophobia.

A psychophysical study was performed in migraineurs with normal eyesight to test the effects of colors on headache intensity and other headache features,[42] it was found that green light significantly attenuated the headache intensity. Through color selective electroretinography and analysis of visual evoked potentials in migraineurs, it was shown that the perception of headache intensity is selectively modulated by spectral light through photoactivation of cone-driven retinal pathways.[50] Similarly, a study focusing on green light analgesia in arthritic mice showed that cone-dominated retinal inputs mediated green light analgesia.[5] One study evaluated the sensitivity of the visual system in migraine patients and control subjects, and revealed that retinal cones or the visual cortex did not induce inherent hypersensitivity to light.[51]

Intrinsically Photosensitive Retinal Ganglion Cells

The neural retina has a layered structure. Rods and cones, the first-order neurons in the visual pathway, initiate the transduction process of visual signals, which are subsequently transmitted to RGCs.[52] Intrinsically photosensitive retinal ganglion cells are not only extrinsically activated by rods and cones,[53,54] but also intrinsically by virtue of their unique photopigment known as melanopsin. Intrinsically photosensitive retinal ganglion cells have been reported to mediate light signals involved in bright light–induced antinociception.[31,55] Hu et al[4] found that bright light regulates nocifensive behaviors in mice through a visual circuit. They demonstrated that ON-type RGCs directly innervate the downstream pathway, mediating the antinociceptive effects. Surprisingly, a study showed that exacerbation of migraine headache by light was preserved in blind patients who could sense light in the face of severe degeneration of rod and cone photoreceptors.[56] Photomodulatory effects are exerted by novel axonal projections of RGCs that converge to the posterior region of the thalamus consisting of axons of ipRGCs.

These studies elucidate the exact photoreceptor class responsible for light-induced analgesia.

Brain Regions and Circuits Associated with Photoanalgesia

Retinal projections of rods and cones to the brain constitute imaging and nonimaging pathways. Images are formed primarily by activation of corn RGCs, and the functions of the nonimaging pathway are all mediated by a specialized pathway originating from ipRGCs, whose axons project via the optic nerve to the ventral suprachiasmatic nucleus (SCN), intergeniculate leaflet (IGL)/lateral geniculate nucleus (LGN), and olivary pretectal nucleus (OPN).[57–59] These brain regions, which may be involved in photoanalgesia, are introduced below (Figure 2).

Suprachiasmatic Nucleus

The suprachiasmatic nucleus is a compact, bilaterally paired cell group in the anterior–ventral hypothalamus. It was first identified as a hypothalamic retinal target in rodents, and by implication it was considered as a potential circadian control point following autoradiographic visualization of its dedicated route of retinal innervation—the retina hypothalamic tract.[60] In mammals, it is the site of an endogenous pacemaker that regulates circadian rhythmicity and plays an indispensable role in behavioral, physiological, and hormonal rhythms in response to the environmental light–dark cycle.[3,61] Suprachiasmatic nucleus also appears to function as a seasonal clock underlying the measurement of daylength.[62] In summary, the SCN is the clock and calendar of vertebrates.

Suprachiasmatic nucleus participates in photoanalgesia probably by projecting to the pineal gland (PG)[62,63] and the paraventricular nucleus (PVN).[64,65]

The pineal gland secretes the hormone melatonin.[66] Melatonin synthesis follows a daily rhythm, with high levels during night time and low levels during the day time, to regulate the daily rhythms. Melatonin is essential for the

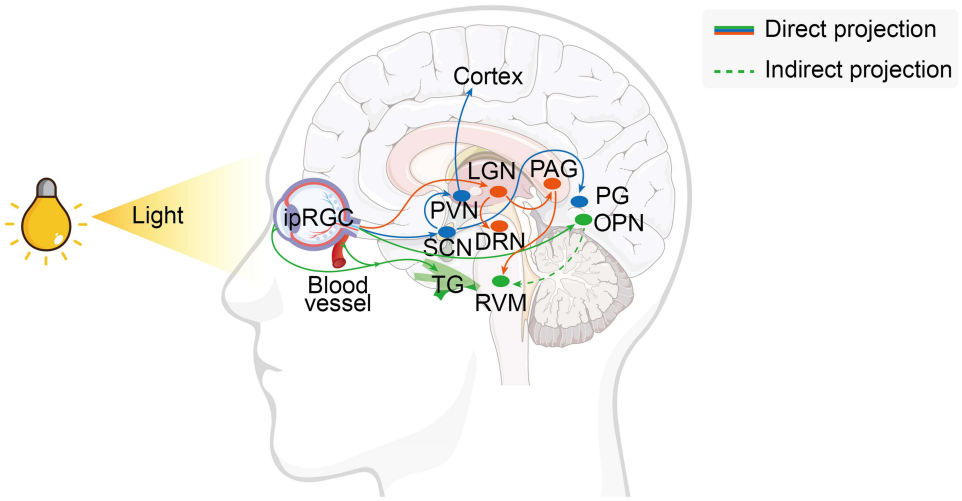

Figure 2 Illustration of brain regions and circuits associated with photoanalgesia.
Abbreviations: PG, pineal gland; SCN, suprachiasmatic nucleus; PVN, paraventricular nucleus; OPN, olivary pretectal nucleus.

integration of seasonal photoperiodic changes in physiology.[67] A large body of evidence suggests that melatonin has antinociceptive effects in CP conditions, including migraine headache,[67] fibromyalgia,[68] irritable bowel syndrome,[69] and temporomandibular joint osteoarthritis-induced CP.[70] Similarly, Yang et al[71] found that intrathecal administration of melatonin changed inflammatory cytokine levels to attenuate bone cancer pain, so they proposed that melatonin may be a promising drug for the clinical treatment of bone cancer pain (Figure 3A).

The paraventricular nucleus is another nucleus which the axons of the SCN project to.[64,72] Its magnocellular neurons project mainly to the posterior lobe of the pituitary gland, where they secrete oxytocin (OXT) into the blood and the hypothalamic-neuron hypophysial system,[73] as the parvocellular neurons project to the cortex[74] (Figure 3B). Repeated OXT administration has been reported to play an analgesic role in preventing central sensitization by regulating synaptic plasticity in a chronic migraine mouse model.[72] There is circumstantial evidence that OXT might be involved in migraine headache. The level of circulating OXT increases over the course of pregnancy,[75] and the frequency of migraine headaches decreases inversely.[76] Consistent with this observation, compared to migraineurs who bottle feed, migraineurs who breastfeed have higher circulating levels of OXT[77] and demonstrate a lower rate of postpartum migraine recurrence.[76] An experiment on the nocifensive behavior of zebrafish showed that OXT neuron activation is sufficient to generate this defensive behavior, whereas ablation of OXT neurons attenuates this behavior, indicating that OXT neurons are crucial for the generation of appropriate analgesic responses to noxious input. The results of a similar study also showed that evoked OXT release from these OXT neurons suppresses nociception and promotes analgesia in an animal model of inflammatory pain.[78,79] These data highlight that OXT neurons of the PVN regulated by ipRGCs may play a potential role in photoanalgesia regulation.

Intergeniculate Leaflet/Lateral Geniculate Nucleus

The rodent ventral LGN (vLGN) and IGL in the visual thalamus are homologous to the primate pregeniculate nucleus.[31] The IGL/LGN of the thalamus is the core retinorecipient structure implicated in orchestrating circadian rhythmicity. The IGL/LGN network is highly GABAergic and consists mainly of neuropeptide Y-synthesizing and enkephalinergic neurons.[5,31] Enkephalinergic neurons have been reported to provide network inhibition.[80] The GABAergic neurons of the IGL/LGN project to the periaqueductal gray area (PAG),[81] which is an evolutionarily conserved neurosubstrate providing a key link to the regulation of nocifensive behaviors.[82,83] These studies demonstrated that bright light treatment activates the retina–IGL/LGN–PAG pathway, producing antinociceptive effects. Similar to the IGL/LGN, it has been found that green light exposure for several consecutive days can significantly relief complete Freund's adjuvant-induced thermal hyperalgesia and mechanical allodynia in mice.[5] To verify the role of this pathway in their study, they inhibited the retina–IGL/vLGN pathway and completely abolished the analgesic effects, which showed that the retina–IGL/vLGN pathway is responsible for the green light

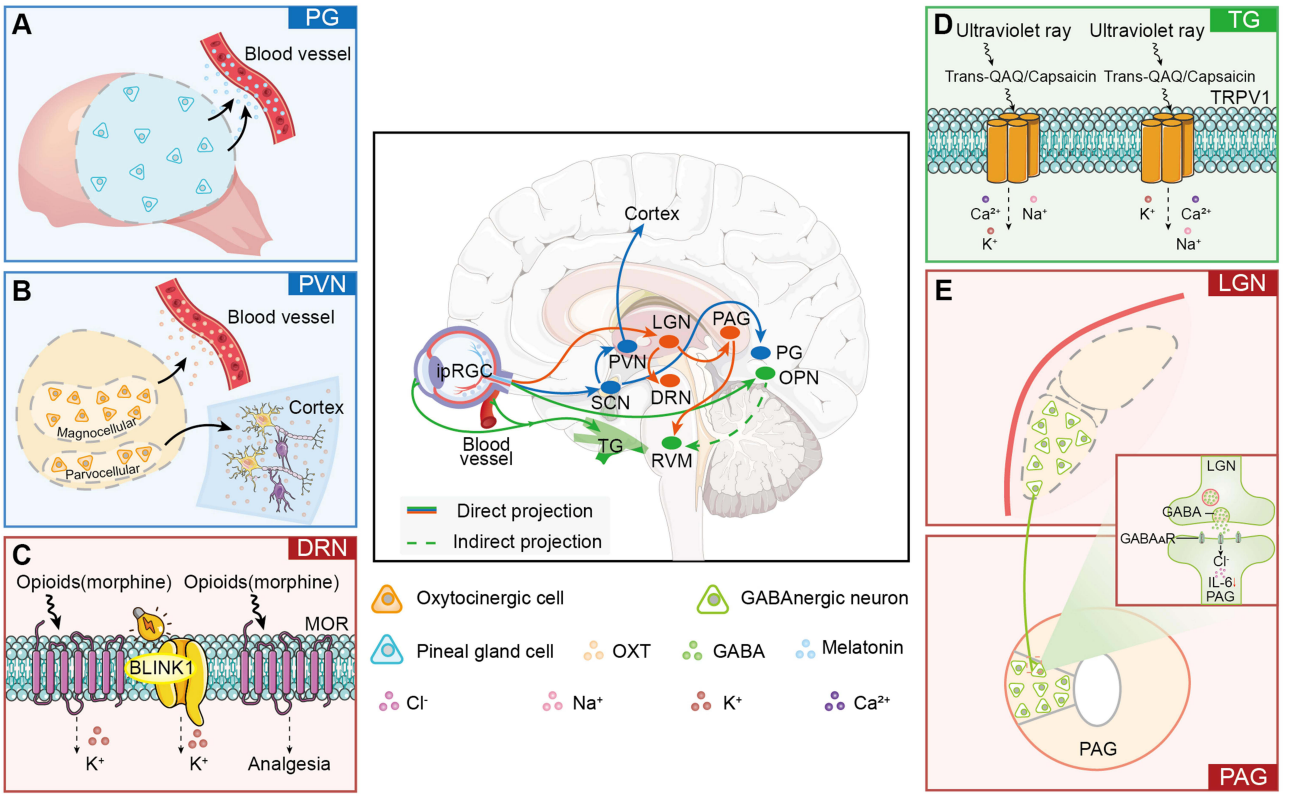

Figure 3 Summary of the targets involved in photoanalgesia. (**A**) The pineal gland exerts analgesic effects by releasing melatonin. (**B**) Different cell types and projections of OXT secreted by the PVN. (**C**) Schematic diagram showing how MOR and BLINK participate in analgesia through K^+ channels in the DRN. (**D**) Schematic diagram of TRPV1 as a nonselective cation channel playing an analgesic role in the TG system. (**E**) Schematic diagram showing how the GABAergic system plays an analgesic role in the LGN-PAG circuit.

Abbreviations: GABA, γ-aminobutyric acid; MOR, μ-opioid receptor; QAQ, quaternary ammonium-azobenzene-quaternary ammonium; TRPV1, transient receptor potential ion vanilloid receptor 1.

analgesia, and they showed that the IGL/vLGN–dorsal raphe nucleus (DRN) is the crucial region for photoanalgesia as well. Besides, there is another study indicating that morphine plays an analgesic role through stimulating the retina–geniculate–cortex pathway and the thalamus–cortex circuit by regulating the opioid receptors.[84]

Olivary Pretectal Nucleus

The olivary pretectal nucleus has classically been recognized as a relay in the pupillary light reflex,[85,86] which is also an important target of ipRGCs. A study focusing on photosensitivity explored the brain regions that are activated by light, and it was found that pain-modulating neurons in the rostral ventromedial medulla (RVM) unexpectedly respond to light; approximately half of the pain-facilitating "ON-cells" and pain-inhibiting "OFF-cells" sampled exhibited a change in firing with light exposure, shifting the system to a pronociceptive state. The change in neuronal firing was blocked by inactivation of the OPN.[35] This means that the OPN is a crucial brain region for photosensitivity. But this finding also implies that light-evoked responses in the RVM do not represent a noxious ocular event, which would presumably be mediated by the trigeminal (TG) system. The role of the TG system in facial and dural sensitivity has been recognized for a long time. Moreover, the TG system has also been considered a prominent actor in brain nociceptive innervation. It is the anatomical substrate of several frequent conditions, such as primary or secondary headaches,[87] TG neuralgia,[88,89] and other orofacial pains,[90] as well as ocular pain.[91]

Targets Associated with Photoanalgesia

Considering the importance of the characteristics of light-sensitive cells, such as ipRGCs, a novel cross-integration discipline has been developed, optogenetics, whose basic concept is the manipulation of the activity of live cells which generate light-sensitive proteins (opsins) by transducing electrical currents.[92,93] This technology has revolutionized the

study of neuroscience with single-cell and millisecond precision control of neurons.[94] It is possible to manipulate neuronal excitability and network activity to exert analgesia effects in vertebrates. Several potential targets are related to photoanalgesia (Figure 3).

Ion Channel Targets Related to Photoanalgesia

Ion channels such as sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), and chloride (Cl^-) channels are transmembrane proteins that control the movement of ions across the cell membrane. They affect cellular activity and their permeability is closely related to many life activities, such as the occurrence of receptor potentials, nerve excitation, and regulation of the central nervous system. Nociceptor nerve terminals express ligand-gated and voltage-gated ion channels, which are key molecular transducers of these noxious stimuli.[95] For this reason, the generation of photosensitivity proteins in neurons can regulate their activity via ion channels. Researchers conducted a series of studies and found that light changes the state of ion channels through photosensitive proteins to regulate the excitability of cells and exert analgesic effects through downstream molecules. We highlight some known receptors that can change the state of ion channels below.

μ-Opioid receptors

Opioids have a long cultural and medicinal history, and their best-known member, morphine, has been employed since antiquity to alleviate pain and induce euphoria.[96] μ-Opioid is an opioid subtype and μ-Opioid receptors (MORs) are widely distributed in the DRN.[5] Opioid receptors belong to family A of the GPCRs, which includes many important drug targets.[97] GPCRs of this type are closely related to the opsin photoreceptors, which enable vision and shape the circadian rhythm in humans.[98] The MOR is the major target of morphine. K^+ plays a crucial role in triggering termination of action potentials (APs) and makes a major contribution to maintaining the resting potential. Alberio et al[99] investigated light-gated K^+ channels and then engineered the light-gated K^+ channel BLINK, whose activity is controlled by blue light (455 nm) (Figure 3C). A study from the same group later showed that BLINK has favorable properties for optogenetics. BLINK is an inhibitory tool in long-lasting optogenetic experiments, and activation by light reduced pain in a rat model and inhibited the touch-evoked escape response in zebrafish.[100] Subsequently, a MOR was generated that is activated by G-protein-coupled inward rectifier channels, which initiate a quick K^+ influx upon exposure to blue light, and photo-analgesics were developed, such as the azobenzene derivative of fentanyl.[101]

TRPV1 Receptors

Transient receptor potential ion vanilloid receptor 1 (TRPV1), a nonselective voltage-gated cation channel known for its role in nociception, is the most studied of the transient receptor potential ion channels.[102,103] TRPV1 channels are highly expressed in pain fibers but scarcely present in the central nervous system.[104–106] They are involved in the transduction of pain stimuli from the periphery towards the central nervous system.[106] They are expressed in sub-populations of sensory nerve fibers within the dorsal root and TG ganglia.[107]

Capsaicin is a specific exogenous TRPV1 agonist. Cis-AzCA4 is the azo derivative of capsaicin that was found to be the most effective in activating TRPV1. Photoactivation of TRPV1 with this compound is reversible and has been achieved in both human embryonic kidney 293 T lymphocyte cells and C fibers. TRPV1-positive neurons of the dorsal root ganglion in mice selectively respond to photoactive TRPV1. In vivo tests demonstrated a TRPV1-mediated hyperalgesia by this photo-compound.[108,109] Moreover, the first example of fusion of photo-pharmacology and lipid signaling with potential application in controlling protein–lipid interactions has been presented.[109]

Based primarily on the characteristics of TRPV1, a nonselective cation channel that is highly expressed in pain fibers, the molecular mechanism underlying the initiation and propagation of APs is the opening and closing of voltage-gated ion channels.[110,111] When excitatory inputs to a neuron trigger a depolarization above the AP initiation threshold, voltage-gated Na^+ channel quickly open and Na^+ ions rush into the cell, depolarizing the membrane even further. Quaternary ammonium-azobenzene-quaternary ammonium (QAQ) is a photo-switchable compound developed on the basis of lidocaine, a local anesthetic that blocks voltage-gated channels.[112,113] QAQ prevents AP firing when neurons receive excitatory inputs by blocking all voltage-gated K^+, Na^+, and Ca^{2+} channels (Figure 3D). The team of Mourot[112] found that QAQ was able to enter cells through open TRPV1, enabling the targeted photosensitization of cells expressing either of these channels.[113] As TRPV1

channels are heat-activated channels required for the detection of noxious heat,[103] QAQ can play an inhibitory role for nociceptors that are selectively regulated by light.[112,113]

$GABA_A$ Receptors

γ-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian brain. $GABA_A$ receptors are pentameric ligand-gated ion channels that are activated by GABA.[114] Binding of GABA results in the opening of a Cl^- selective pore. Following this interaction, Cl^- influx is promoted, while postsynaptic neuron hyperpolarization and action-potential firing decrease (Figure 3E). The gabapentinoids, which are GABA analogs, are frontline therapeutic agents for neuronal pain that can act directly in the spinal cord to suppress nociception and pain aversiveness.[115] In rat models of neuropathy, gabapentinoids reverse tactile and thermal allodynia.[116] Thus, $GABA_A$ receptors serve as targets for anesthetic, hypnotic, and anticonvulsant drugs.[114]

$GABA_A$ receptors are not sensitive to light. Nevertheless, photo-switchable agents have been produced that can switch GABAergic neurons between an active and an inactive form by the application of light.[117] The trans isoform of this compound was found to be capable of activating a $GABA_A$ receptor subunit, and the cis isoform was found inactive. Whole-cell patch clamp recording of HEK cells with the trans isoform also showed that exposure to light leads to conversion to its cis isoform and decreases the current amplitude. On the contrary, a dark environment could increase the current. The anesthetic activity of photo-switchable agents was investigated in albino *Xenopus laevis* tadpoles, and it was found that anesthesia could be achieved.[117] This study demonstrated that light potentiates GABA-induced Cl^- currents and that light-dependent anesthetic agents can be used effectively. These studies showed that the $GABA_A$ receptor is the target of photoanalgesia.

Immune Targets and Pathways Related to Photoanalgesia

As mentioned, Chronic pain is classified into three main categories: nociceptive, neuropathic, and nociplastic.[9] A common pathogenic cause of CP is dysregulation of the immune system. Many reports showed that the immune system is strongly correlated with CP. For example, Goebel et al[118] showed that IgG from fibromyalgia syndrome (FMS) patients produced sensory hypersensitivity by sensitizing nociceptive neurons. Mice treated with IgG from FMS patients displayed increased sensitivity to noxious mechanical and cold stimulation, and nociceptive fibers in skin-nerve preparations from mice treated with FMS IgG displayed an increased responsiveness to cold and mechanical stimulation. Transfer of IgG-depleted serum from FMS patients or IgG from healthy control subjects had no effect, indicating that therapies reducing IgG titers may be effective for fibromyalgia. Considering that interleukin (IL)-1β is a critical cytokine involved in creating heightened nociception associated with persistent pain, Arman et al[119] used chronic constriction injury (CCI) to initiate nerve injury in rats and then quantified intrathecal IL-1β concentrations. They found that the degree of mechanical allodynia was positively correlated with the increase in the intrathecal concentration of IL-1β in CCI animals, providing a molecular biomarker of the degree of exaggerated pain. Recently, a study showed that mice exposed to four days of dim light (5 lux) at night exhibited cold hyperalgesia, and mice exhibited both cold hyperalgesia and mechanical allodynia after 28 days. This phenotype was concurrent with upregulated IL-6 and nerve growth factor mRNA expression in the medulla and elevated MOR mRNA expression in the PAG.[33] In a recent study, optogenetic or chemogenetic activation of the glutamatergic neurons of the secondary visual cortex ($V2M^{Glu}$) to GABAergic neurons in the anterior cingulate cortex (ACC) was performed, which inhibits local glutamatergic neurons ($ACC^{GABA\text{-}Glu}$), mimicking green light-induced antinociception in both neuropathic and inflammatory pain model mice. Artificial inhibition of ACC-projecting $V2M^{Glu}$ neurons abolishes the antinociception induced by green light.[7] This means that the V2M-ACC circuit is a potential candidate mediating green light-induced antinociceptive effects to treat immune pain. These results provide circumstantial evidence explaining how green light exerts analgesic effects in immune-related CP. Summarizing these experimental results, we believe that there is a connection among light, immunity, and pain.

Conclusion and Prospect

Chronic pain is associated with alterations in the peripheral and central nervous system, along with a decline in the quality of life.[120,121] It is caused by multidimensional, dynamic interactions among biological, psychological, and social factors that reciprocally influence each other.[122] As a leading cause of disability and a potential factor that affects biological processes, CP causes a heavy financial burden.[9] Chronic pain affects family relationships and self-esteem of patients, and is associated with

a reduced life expectancy, and leads to higher suicide rates and a higher substance abuse risk.[123,124] Current methods of pain management involve pharmacotherapy using agents such as serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, nonsteroidal anti-inflammatory drugs, corticosteroids, benzodiazepines, gabapentinoids, and opioids, but these drugs cause concerning side effects, such as sedation, cardiotoxicity, ataxia, addiction, and respiratory depression.[125] For this reason, there has been a growing desire to develop drugs with high efficiency and lower/no side effects and nonpharmacologic methods to manage and relieve pain. In this review, we discussed retinal photoreceptors and their functions in the photo-response. We described brain regions (including the SCN, IGL/LGN, and OPN) and circuits that ipRGCs project to, and we illustrate the evidence showing these regions are involved in photoanalgesia. In order to further explain the mechanisms underlying photoanalgesia, we introduced various potential targets associated with photoanalgesia. We aimed to provide a foundation to understand the mechanisms underlying CP and develop light-based novel analgesic treatment methods. This review may provide an opportunity to drive the field towards future translational, clinical studies and support pain drug development.

Light is a widely recognized effective analgesic which exerts its effects through the visual pathway. Numerous reports in the past decade have documented the mechanisms of pain modulation by light. Beside the therapeutic effects on pain, light of certain colors may also exacerbate clinical pain, such as fibromyalgia and migraine. For example, white, blue, amber, and red light increase pain, while green light decreases pain, probably because the photoanalgesic mechanism is different between skin and eyes:[126] cutaneous application acts primarily via peripheral nerves, whereas visual application acts via the central nervous system. Red and near-infrared light are administered cutaneously with seconds to minutes of exposure, whereas green and bright white light are administered visually with much longer duration of exposure. Red and near-infrared light have large wavelengths (625−740 nm and 750−1000 nm), which allows for very high tissue penetrance.[127] Because of this property, the duration of light exposure for red and infrared light treatments to cause photo-biomodulatory effects is short. Green light (500 −565 nm) has a much shorter wavelength; therefore, it may be insufficient to penetrate the skin, but it exerts analgesic effects through the visual pathway. Also note that ipRGCs, which produce melanopsin, have a peak spectral sensitivity of 480 nm (blue/cyan). Bright white light, which contains light of all wavelengths in the visible spectrum, can exert analgesic effects. As green light, bright white light treatment works through the visual pathway, requiring exposure for several hours.[28–31,41] However, one main difference between these two colors is the intensity at which the light is administered. Bright white light therapy is typically administered at >3000 lux and even at 5000 lux in one study.[41] On the contrary, green light therapy is administered at 4–110 lux.[5,6,38,40] The high tissue penetrance of red and near-infrared lights may induce thermal injury, but no adverse effects have been reported in any clinical or animal studies of visual light therapy. Based on these findings, visual light exposure can be a useful analgesic therapy. It provides a safe and effective option to reduce the physical, psychological, economic, and societal burden on patients who are beset with acute pain and CP. However, the reason why light with different characteristics leads to different analgesic effects is still unclear.

Recently, the use of light as a novel nonpharmacologic treatment for several pain syndromes has become particularly attractive to both clinicians and patients due to its noninvasiveness and lack of side effects, ultimately increasing patient compliance. Light changes the activity of live cells which generate light-sensitive proteins to play a role of abirritation. The novel cross-integration discipline of optogenetics has been established; as the name suggests, optogenetics is the integration of two fields: optics and genetics (the optics part is associated with illumination with a specific light spectrum, whereas the genetics part is associated with the expression of the modified opsin protein in cells). Based on this technology, photo-pharmacology has come into being. Photo-pharmacology deals with photo-responsive agents that exert analgesic effects when a switch occurs between two (cis–trans) or more isoforms. So far, targets for these agents range from ion channels and GPCRs to transporters, enzymes, and lipids.[128] Hence, the biological functions can be controlled by acting on native receptors or acceptors.[108,128,129] The photo-pharmacology principle holds an advantage of selectivity because light can be delivered with a high precision in terms of its intensity and wavelength for adjustable dosing.[108,128,129] The possibility to alter the activity of a drug by light offers several advantages, such as reducing off-target, systemic side effects or even drug resistance,[108] which provides a powerful potential for clinical transformation.

In the past few decades, nanosized polymeric micelles have emerged as promising drug delivery carriers due to their outstanding characteristics, including high drug loading capacity, long circulation in the bloodstream, and passive targeting capability based on the enhanced permeability and retention effect.[130] An ideal nanocarriers combines efficient and stable drug encapsulation while possessing the unique features of releasing substances or molecules upon application of a specific external

stimulus. In typical systems, conformational changes of nanocarriers are stimulated by classical triggers such as pH[131] and temperature.[132] Nevertheless, these systems often suffer from spatial restrictions and/or inefficient disruption/swelling of the nanocarrier wall. Aiming to address this problem, researchers have invented a kind of capsule whose wall has been doped with irradiation dyes, and its properties can be reversibly altered by applying a specific wavelength stimulus.[133] The applications of this technology include the treatment of many diseases, including pain. For example, a novel concept has been introduced to fabricate a two-photon-sensitive and sugar-targeting nanocarrier which can contain a clinical anticancer drug, doxorubicin, to be released in a controlled manner by changing the irradiation time.[134] Another anti-cancer study based on similar principles and techniques is that by Meng and coworkers,[135] who invented a chitosan-based nanocarrier which exhibits a dual response to pH and light. Optical control nanocarrier technology is also widely used in ophthalmic diseases. The aim is to employ a delivery method to deliver a photosensitizing compound selectively to the target tissue.[131,136] Liu and coworkers[137] explored a light-sensitive nanocarrier for simultaneous triggered antibiotic release. Another important research field of optically controlled nanocarrier technology is nanocarrier-mediated RNA interference therapeutics,[138,139] which has become a promising way to treat numerous human diseases caused by genetic factors. These studies have proved that light can be used to treat clinical diseases and reveal a broad prospect for phototherapy.

Pain is associated with both psychological and biological changes and with alterations in both the peripheral and the central nervous system. In the future, we can pay more attention to (i) research the long-loop circuit of photoanalgesic, (ii) fully explain the mechanism of photoanalgesia, including the photoreceptors in the eyes and their connections with pain-related brain regions, such as the TG system and PAG, and (iii) identify the specific pain receptors on the body surface. At present, the underlying mechanisms of photoanalgesia have yet to be fully elucidated. Pain is a subjective feeling accompanied by substantial or potential tissue damage, and the pathological mechanism is influenced by central and peripheral factors. When we try to find the targets of photoanalgesia, perhaps it can be considered from the comorbidity of pain and emotion, such as comorbid depression and CP[140–142] or pain on opiate addiction.[143] It suggests that when we look for targets of pain, we should not only focus on the physiological molecules related to pain, but also broaden our horizons to the targets of psychological diseases, such as brain-derived nerve factor (*BDNF*),[144,145] serotonin (5-hydroxytryptamine; 5-HT),[146–148] and dopamine.[149,150] Considering these factors together may aid in elucidating the mechanisms underlying photoanalgesia.

The promising results from preclinical studies of phototherapy in animals and clinical studies in patients reveal that light can modulate pain. Light may provide more possibilities for disease treatment in the future.

Acknowledgments

This study was supported by the National Natural Science Foundation of China (no. 82274383, 81974553 and 82004078), the Special Funding for Taishan Scholars Project (no. tsqn202211137), the Natural Science Foundation of Shandong Province (nos. ZR2020ZD17 and ZR2021LZY018), the Chinese Medicine and Brain Science Youth Scientific Research Innovation Team, Shandong University of Traditional Chinese Medicine (no. 22202101), High Level Key Disciplines of Traditional Chinese Medicine: Basic Theory of Traditional Chinese Medicine, National Administration of Traditional Chinese Medicine.

Disclosure

The authors report no conflicts of interest in this work.

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