Review Article

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The application of optogenetics in traumatic brain injury research: A narrative review

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Abstract:

Optogenetics has revolutionized the landscape of research on neurological disorders by enabling high spatial specificity and millisecond-level temporal precision in neuroscience studies. In the field of traumatic brain injury (TBI), optogenetic techniques have greatly advanced our understanding of the pathological and physiological processes involved, providing valuable guidance for both monitoring and therapeutic interventions. This article offers a review of the latest research applications of optogenetics in the study of TBI.

Keywords:

Impairments, opsins, optogenetics, pathophysiology, traumatic brain injury

Introduction

Traumatic brain injury (TBI) refers to damage to brain tissue and function caused by external forces acting on the head. Clinically, TBI is classified into mild, moderate, and severe categories based on the extent of injury severity.[1] TBI has the highest incidence among all common neurological disorders. It is not only an acute condition but also a chronic one with long-term sequelae.[2] Globally, over 50 million people are affected by TBI each year,[3] and 43% of survivors experience disability.[4] The economic burden of TBI is estimated to be around $400 billion annually worldwide.[5] The primary mechanism of TBI involves the sudden stretching and tearing of axons due to trauma, resulting in diffuse axonal injury.[1] Following TBI, pathological changes occur, including vasospasm, blood–brain barrier disruption, cerebral edema, altered brain cell metabolism, and disturbed calcium ion balance.[6,7] Depending on the severity of brain tissue damage, clinical manifestations such as nausea, vomiting, headache, emotional abnormalities, cognitive impairment, altered consciousness, motor dysfunction, and sensory impairments may occur,[3] imposing a significant health burden on patients.

The neuronal structure and function of the brain are highly complex. Traditional methods have limited spatial and temporal precision in studying the pathological mechanisms of TBI.[8] Current clinical monitoring techniques for TBI mainly include intracranial pressure monitoring, brain temperature monitoring, electroencephalogram (EEG) monitoring, and brain microdialysis monitoring,[9] but they do not involve monitoring of brain damage at the neuronal and vascular levels. In addition, in terms of functional recovery after TBI, treatment options include traditional therapies (such as physical therapy, speech therapy, and neuropsychological therapy),[10] medication,[10] virtual reality technology,[11] hyperbaric oxygen therapy,[12] transcranial magnetic stimulation, transcranial direct

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current stimulation, and deep brain stimulation.[13] However, these therapies currently suffer from the lack of specific treatment targets. In recent years, the emergence of optogenetics has made it possible to precisely activate or inhibit specific cell types and neural circuits with high spatiotemporal accuracy. This technique has been widely applied in research on neurological disorders, including stroke,[14] epilepsy,[15] depression,[16] and Alzheimer's disease.[17] In the field of TBI, optogenetics has promoted the development of research on TBI pathophysiology, brain injury monitoring, and treatment.

Optogenetics

Optogenetics is a multidisciplinary field that encompasses biology, genetics, and optics. It revolutionized brain research when it was first applied in mice in 2007.[18] The technique involves introducing genes encoding specific opsins, along with other tool genes such as fluorescent proteins and promoters, into target cells using gene editing or viral transfection methods. This enables the expression of the corresponding proteins in specific neurons. To activate the opsins, an optical source is surgically implanted into the brain of experimental animals. This allows the opsins to be activated using specific wavelengths of light. The stimulation can either excite or inhibit the target neuronal cells, depending on the type of opsins used. The activity of the target neurons is then recorded using techniques such as two-photon fluorescence microscopy[19] and patch clamp techniques.[20] Optogenetics provides high spatiotemporal resolution, allowing for precise and rapid manipulation of specific cells and neural circuits. It has become a powerful tool in neuroscience, greatly advancing our understanding of neural disease mechanisms and facilitating the exploration of new therapeutic targets.[21]

Opsins

Opsins are a class of proteins that can sense light signals and undergo conformational changes in response.[16] In 2005, Boyden *et al*.[22] pioneered the application of opsins in neuroscience using ChR2 to control the activity of cultured hippocampal neurons on a millisecond timescale. Since then, the field of optogenetics has expanded with the development of new opsins, subtypes, and variants. Upon expression in target cells, opsin proteins can depolarize or hyperpolarize these cells upon activation by light of specific wavelengths, depending on the type and structure of the opsins. Some commonly used opsins include ChR2, NpHR, and Arch, among others (refer to Table 1 for more examples). These opsins can be utilized in combination as well. For instance, the optogenetic tool BiPOLES, developed by Vierock J *et al*.,[23] combines the opsins GtACR2.1 and ChrimsonR. It enables bidirectional control of neuronal activity through the use of two different wavelengths of light in various animal model systems.

Introduce opsin gene

To express the required opsins in target cells, the relevant genes need to be introduced into these cells. Currently, viral transfection[32] and transgenic technology[33] are the main methods used to achieve this process. Among them, viral transfection is more widely used, with commonly used viral vectors including lentivirus and adeno-associated virus (AAV).[34] AAV is preferred by many researchers due to its nonpathogenic nature, ability for safe and long-term expression, self-sufficiency without the need for auxiliary viruses, stable maintenance of the phenotype, and efficient transduction within a given volume.[35-37]

Activate opsins

Once opsins are successfully expressed in target neurons, it is necessary to design an implant that can deliver light to specific regions of the brain for activating these neurons. Currently, many optogenetics experiments utilize high-power fiber-coupled lasers. However, these lasers have certain drawbacks, including high-power requirements, limitations on the natural behavior of experimental subjects, and the potential generation of local heat.[38] In recent years, new types of implants have

Table 1: Commonly used opsins in optogenetics

Opsins	Description	Mode	Light wave lengths (nm)	References
ChR2	Derived from the green algae *Chlamydomonas reinhardtii*, cation channel	Excitatory	470	Boyden *et al*., 2005[22]
VChR1	Derived from the green alga *Volvox carteri*, cation channel	Excitatory	589	Zhang *et al*., 2008[24]
ChETA	Mutated ChR2 variant	Excitatory	500	Gunaydin *et al*., 2010[25]
ChIEF	Chimeric ChR1/ChR2 variant	Excitatory	450	Lin *et al*., 2009[26]
C1V1	Chimeric ChR1/VChR2 variant	Excitatory	540	Erbguth *et al*., 2012[27]
NpHR	Derived from the halophilic archaeon *Natronomonas pharaonis*, chloride pump	Inhibitory	590	Zhang *et al*., 2007[28]
eNpHR3.0	Mutated NpHR	Inhibitory	590	Gradinaru *et al*., 2008[29]
Arch	Derived from *Halorubrum* sodomense, proton pump	Inhibitory	566	Chow *et al*., 2010[30]
Mac	Derived from the fungus *Leptosphaeria maculans*, proton pump	Inhibitory	550	Husson *et al*., 2012[31]

NpHR: Halorhodopsin

emerged as alternatives. For example, miniaturized light emitting diode (LED) arrays based on flexible polyimide[39] and multichannel flexible optoelectronic fiber devices[40] have been developed. These advancements aim to address challenges such as the need for smaller implant sizes, appropriate spatial resolution, high safety standards, and strong controllability.[41] The development of implantable devices that meet these requirements remains a key challenge in the field of optogenetics. Researchers continue to explore innovative approaches to further improve the performance and functionality of optogenetic implants, enabling more precise and safe manipulation of neural circuits in future experiments.

Label and track target neurons

The main tools for labeling and tracking target neurons include genetically encoded calcium indicators (GECIs), genetically encoded voltage indicators (GEVIs), neurotransmitter sensors, and fluorescent markers. GECIs are capable of monitoring changes in calcium ion concentrations during neuronal activity, allowing for calcium imaging in specific brain regions and generating fluorescence signals indicative of calcium levels.[42] Similarly, GEVIs are sensitive to changes in cellular membrane potential. They undergo conformational changes and produce proportional fluorescence signals when there are alterations in neuronal membrane potential, enabling researchers to track these changes in real time.[43] Neurotransmitter sensors are specifically designed to monitor the release of neurotransmitters. They can be classified into two categories: periplasmic-binding protein (PBP)-based sensors and G-protein-coupled receptor (GPCR)-based sensors. PBP-based sensors selectively bind to target neurotransmitters, and when the target neurotransmitter binds to the PBP, there is a conformational change in the protein, resulting in fluorescence signals. GPCR-based sensors involve the genetic modification or transfection of target neuronal cells to express GPCRs on their cell membranes. Upon binding of the target neurotransmitter to the GPCR, a series of signal transduction processes occur, often involving fluorescence resonance energy transfer or other fluorescence-based methods, producing fluorescence signals.[44] In addition, fluorescent markers such as EGFP[45] and mCherry[46] are widely utilized in optogenetics to label and visualize specific proteins, subcellular structures, or entire cells in live tissues. These tools are crucial for tracking dynamic processes in living organisms. All these tools require expression in target cells, which is typically achieved through genetic modification or viral transfection, although other methods such as the creation of transgenic animals or *in utero* electroporation can also be employed.

Record neuronal activity

The main equipment for recording and assessing neuronal activity in optogenetics include fluorescence microscopy, patch-clamp technique, and fiber photometry. Fluorescence microscopy utilizes specific fluorescent probes or labeled proteins to visualize and study biological processes in cells and organisms.[19] Two-photon fluorescence microscopy, in particular, has gained widespread use due to its advantages of enhanced excitation penetration, high fluorescence collection efficiency, and low photobleaching and photodamage, making it ideal for deep tissue imaging.[47] The patch-clamp technique is a commonly used experimental technique in cellular physiology research. It involves using a glass micropipette with a sharp tip filled with artificial intracellular fluid and mounted onto recording equipment. The micropipette is then pressed onto the cell membrane, forming a cell-attached configuration, which allows researchers to record neuronal membrane potentials and currents with high resolution, this technique can be applied in various configurations such as cell-attached, whole-cell, inside-out, and outside-out patches, providing detailed insights into ion channel function.[20] Fiber photometry is widely used in optogenetics to monitor neuronal activity *in vivo*. It involves surgically implanting a small optical fiber above the target brain region. The fiber collects fluorescence signals generated by GECIs (such as Genetically Encoded Calcium Indicator with a Green Fluorescent Protein (GCaMP)) or neurotransmitter sensors in the target neurons during the experiment, enabling real-time monitoring of their activity.[48]

The Application of Optogenetics in Traumatic Brain Injury

Applications in brain function assessment and monitoring after traumatic brain injury

Currently, in clinical practice, the severity and prognosis of brain injuries are primarily assessed using a combination of relevant scales and imaging techniques such as the Glasgow Coma Scale, computed tomography, magnetic resonance imaging, and magnetic resonance angiography.[49] While these methods have significant clinical value in diagnosing post-TBI brain injuries, they cannot provide both high spatial resolution and high temporal accuracy simultaneously. Recently, several studies have employed optogenetic techniques in mouse models of TBI to enable real-time monitoring of microscopic secondary brain changes. While research in this field remains limited and largely focused on animal models, these findings hold promise for potential clinical applications of optogenetics in monitoring brain alterations postinjury. For instance, Zhang *et al*.[10] utilized optogenetic methods to develop a tool for monitoring neuronal changes in mouse following TBI, including changes occurring during the TBI process itself. They combined nanotechnology with optogenetics

to create a stretchable transparent electrode array capable of recording real-time neuronal response signals on the surface of the cerebral cortex after optogenetic stimulation. In addition, this carbon nanotube electrode remained functional even during the rapid deformation of brain tissue during the period of brain concussion, allowing for real-time electrophysiological monitoring of neural activity during the injury process. Moreover, in a mouse model of TBI, Nguyen *et al*.[50] combined optogenetics with electromyography to develop optogenetic motor mapping. This involved recording electromyography signals from the biceps brachii muscle while optogenetically stimulating the motor cortex to generate a functional map. The researchers used this method to investigate how changes in cortical excitability in a mouse model of TBI contribute to motor deficits. Their findings revealed that 2 h after TBI, the optogenetically sensitive points in the injured cortex decreased, and the electromyography response amplitude in the biceps brachii muscle significantly decreased. In contrast, in the contralateral cortex, the optogenetically sensitive points increased at 12 h, but there was no significant change in the electromyography response amplitude in the corresponding biceps brachii muscle. Both measurements returned to baseline levels within 24 h. Overall, the real-time capabilities of optogenetics address the limitations of traditional methods and offer valuable insights for monitoring, analyzing, and guiding the treatment of brain injuries.

Applications in the study of traumatic brain injury mechanisms and pathophysiological changes

Neuronal cells

The impact of TBI on brain cells, including primary and secondary injuries, can result in changes in cellular function and even cell death, these injuries are mediated by mechanisms such as inflammation, oxidative stress, and programmed cell death, with excitotoxicity being a particularly significant pathological process.[6] Understanding the mechanisms of neuronal cell changes following TBI is crucial for preventing complications and guiding treatment. Optogenetic technology, compared to traditional research methods, provides precise temporal control in dissecting the dispersed and complex neuronal networks, enabling researchers to gain a clearer and more in-depth understanding of the mechanisms underlying neuronal cell function.[51] The hippocampus is particularly vulnerable in TBI, and resulting hippocampal-dependent cognitive impairment significantly impacts patient prognosis.[52] Current research highlights that post-TBI hippocampal neurodegeneration predominantly affects neurons in the subgranular zone of the dentate gyrus (SGZ-DG).[52] In addition, neuronal damage in the cornu ammonis area I (CA1) region of the hippocampus is also evident,[53] with newly generated immature neurons in the SGZ-DG region being particularly susceptible to TBI-induced effects.[54] In this regard, Kang *et al*.[55] employed optogenetic techniques to stimulate three groups of dentate granule cells (DGCs) at different stages of maturation (neonatally born or born either just before or after TBI). Their findings revealed that optogenetic stimulation enhanced the activation of DGCs born before TBI, leading to increased untransduced DGC feedback inhibition and excitability of parvalbumin-expressing basket cells, other subgroups of DGCs exhibited minimal induction of the aforementioned neural responses. This study elucidated the distinct roles of different subpopulations of DGCs based on their generation dates following TBI. It provides new insights into the potential mechanisms underlying excitability changes after brain injury and offers some references for the prevention and treatment of PTE. In addition, Krukowski *et al*.[56] used optogenetic techniques to examine abnormal neuronal excitability after TBI. They induced optogenetically evoked, PV+-specific inhibitory synaptic currents (oIPSC) to evaluate the performance of oIPSCs in CA1 pyramidal neurons. The researchers found that the amplitude of neuronal oIPSCs was reduced in mouse brain slices after TBI, indicating a decrease in PV neuron-specific inhibitory synaptic transmission in mice after TBI. The studies mentioned above have initially investigated regional differences in hippocampal neuron damage and potential underlying mechanisms following TBI using optogenetic methods. This research offers initial insights into targeted therapies for hippocampal-dependent cognitive impairment after TBI.

Neuronal circuit

Neurons do not exist in isolation; they communicate with each other and form neural circuits through specific patterns of synaptic connections to process information collectively.[57] TBI disrupts these neural circuits, resulting in emotional changes, motor and sensory impairments, and cognitive deficits.[58] Optogenetic technology provides precise control over specific neural circuits, making it valuable for studying their functionality with high spatiotemporal precision. Ndode-Ekane *et al*.[59] utilized optogenetic techniques to investigate the thalamocortical pathway in the mouse model of TBI and analyze the reorganization of axon terminals in the primary somatosensory cortex (S1). The experiment involved applying lateral fluid percussion to the left cortex of mice, the coordinates for fluid percussion were AP(Anterior-Posterior)-4.5 mm from bregma; Medial-Lateral (ML) +2.5 mm over the left cortex. The researchers demonstrated through immunohistochemical analysis that TBI does not alter the spatial distribution or lamina-specific targeting of projection terminals in the primary somatosensory cortex (S1). However, TBI resulted in a 44% decrease in axon terminal density in the motor cortex and a 30% reduction in axon terminal

density in S1. Furthermore, a nematic tensor-based analysis revealed that in TBI rats, the axon terminals in layer V of the cortical area were oriented more parallel to the pial surface. In the experiment involving optogenetic stimulation of thalamocortical relays from the ventral posterior lateral and medial nuclei, TBI rats exhibited a 33% increase in EEG β activity. This indicates a functional alteration in this neural pathway after TBI, specifically an excessive excitatory response of the cortex to thalamic stimulation. In addition to the aforementioned studies, Harris *et al*.[60] used optogenetic techniques and found that within 1 day after mild TBI in mice, somatostatin (SOM) interneurons exhibited increased intrinsic excitability and synaptic efficacy. This may represent the initial stage of self-regulatory attempts in the neocortical network following mild TBI. Furthermore, Nolan *et al*.[61] employed optogenetic techniques and discovered that 2 months after TBI induction in mice, the nonfast-spiking and SOM-expressing subtypes of inhibitory neurons in layer V of the orbitofrontal cortex exhibited reduced intrinsic excitability and decreased prominent output onto parvalbumin-expressing interneurons. This suggests selective disruption of specific inhibitory microcircuits. The above experiments employed optogenetic techniques to reveal changes in neural circuits following TBI, exploring alterations in synaptic function, synaptic spatial structure, and neural network reorganization. They further elucidated the mechanisms underlying excitotoxicity after TBI and the plasticity potential of injured neurons.

Neurovascular

There is a coupling relationship between neurons and blood vessels, where neurons regulate cerebral blood flow by generating signals that directly or indirectly act on local blood vessels such as endothelial cells to elicit vascular responses.[62] Following TBI, disruptions in neurovascular function may occur due to neuronal discharges and diminished evoked potentials in the vicinity of the lesion,[61] as well as neuronal loss.[63] However, current research into neurovascular dysfunction after TBI is limited to resting state or *ex vivo* recordings, and specific functional hemodynamic changes caused by individual blood vessel impairments remain unclear. To investigate neurovascular coupling function, Mester *et al*.[64] used optogenetic techniques to stimulate neurons surrounding target blood vessels. They found that cortical venous blood flow velocity doubled, with an increase in flow velocity of 115 ± 25%. Additionally, the reactivity of cortical veins significantly increased. The area under the curve of the post-stimulus cessation time/cell velocity function curve increased by 53 ± 17% in mice two weeks after TBI modeling. Meanwhile, the spontaneous activity of damaged neurons in the vicinity of the lesion was reduced (neuronal θ power decreases by −57 ± 79%), leading to decreased reactivity (the local field potentials decrease by 47 ± 28%). This study demonstrates that sustained dysregulation of neurovascular function may contribute to long-term brain dysfunction following TBI and provides guidance for the treatment of post-TBI brain dysfunction at the neurovascular level.

Applications in the recovery of impairments

Optogenetics has been extensively utilized in researching impairment recovery in neurological disorders. Initial investigations into the application of optogenetic techniques have also been conducted in mouse models of TBI, ischemic brain injury, and so on, as outlined in Table 2.

Cognitive impairment

TBI can result in cognitive impairments such as attention deficits, memory impairments, and reduced information processing speed.[65] The clinical approaches for improving cognitive dysfunction after TBI primarily involve medication, brain stimulation, and rehabilitation therapies.[45] The emergence of optogenetics has addressed the issue of unclear treatment targets in traditional approaches. Although the therapeutic application of optogenetics is still in the early stages of basic research, it holds great potential. Based on neural stem cells, Zhao *et al*.[45] utilized optogenetic techniques to activate newborn neurons expressing doublecortin (DCX) in the DG of TBI mouse. By optogenetically depolarizing the DCX-expressing neurons during the adult neurogenesis phase, they observed improved survival and maturation of newborn neurons. Notably, depolarization resulted in a reduced latency to find a hidden platform, increased time spent in the target quadrant, and an increased number of platform crossings in the Morris water maze test. These findings indicate enhanced spatial learning and memory functions in TBI mice. Another study conducted by Broussaed *et al*.[66] utilized optogenetics to stimulate pyramidal neurons in the CA1 of the hippocampus, based on the hippocampal theta rhythm. They found that theta rhythm stimulation significantly improved recognition memory in TBI mice, as demonstrated by a notable increase in the time spent exploring novel objects in the novel object recognition test. In summary, optogenetics shows significant potential in the treatment of cognitive dysfunction following TBI, offering a novel perspective for cognitive function therapy.

Consciousness disturbance

Moderate and severe TBI can result in disorders of consciousness (DOC), significantly impacting the prognosis of patients.[70] The treatment methods for DOC following TBI include pharmacological interventions,[71] sensory stimulation,[72] and deep brain stimulation,[73] among others. However, the efficacy of these treatments is not satisfactory. Recent advancements in optogenetics

Table 2: Research utilizing optogenetics to improve impairments

Animal experimental model	Methods for opsins-related gene expression	Opsins	Target neuron	Stimulation protocol	Changes of impairments	References
TBI	Injection of the lentiviral vector carrying the DCX-ChR2-EGFP gene	ChR2	DCX-expressing newborn cells in the DG	After 3–12 days following TBI, blue light stimulation is applied. The stimulation lasts for 15 s, followed by a 30-s pause, and this cycle is repeated three times per day	Improved spatial learning and memory function	Zhao *et al*., 2018[45]
TBI	Injection of AAV serotype 5 carrying the CaMKIIα-ChR2-mCherry gene	ChR2	Hippocampal CA1 pyramidal neurons	After 23 days following TBI, when the animal approached an object during the exploration, blue light stimulation was delivered at theta frequency during 5 min novel location task	Improved recognition memory	Broussard *et al*., 2023[65]
TBI	Injection of AAV carrying the CaMKIIα-ChR2-mCherry	ChR2	Glutamatergic neurons in the paraventricular nucleus of the thalamus	TBI-induced DOC was subjected to blue light stimulation for 5 min	Accelerated the recovery of consciousness	Zhao *et al*., 2023[66]
Ischemic stroke	Thy-1–ChR2–YFP line-18 transgenic mice	ChR2	Layer V of primary motor cortex pyramidal neurons	After a stroke, blue light stimulation is performed from day 5 to day 14. There are three sessions of 1-min stimulation per day, with a 3-min rest period during each session	Enhanced CBF/ neurovascular coupling and functional behavioral recovery	Cheng *et al*., 2014[67]
Ischemic stroke	Injection of AAV carrying the CaMKII-ChR2-mCherry	ChR2	Sensory areas of the brain	After a stroke, from day 5 to day 25, there is a 20-day forearm rehabilitation robot training combined with 3 sessions of 30-s blue light stimulation per day, with a 1-min interval between each session	Boosted the motor functional recovery	Conti *et al*., 2022[68]
Spinal cord injury	Injection of AAV carrying the CaMKII-ChR2-mCherry	ChR2	Pyramidal neurons in the primary motor cortex (M1 area)	After spinal cord injury, from day 5 to day 19, there are three consecutive sessions of 1-min blue light stimulation, with a 3-min rest period in between. This is performed three times a day for a total of 2 weeks	Boosted the motor's functional recovery	Deng *et al*,.2021[69]

EGFP: Enhanced green fluorescent protein, CaMKIIα: Calcium/calmodulin-dependent protein kinase type II alpha, mCherry: Monomeric cherry fluorescent protein, DCX: Doublecortin, TBI: Traumatic brain injury, CA1: Cornu ammonis area I, AAV: Adeno-associated virus, CBF: Cerebral blood flow, DG: Dentate gyrus, DOC: Disorders of consciousness

have provided new insights into the treatment of DOC. Zhao *et al*.[66] conducted a study where they used optogenetic stimulation of glutamatergic neurons in the paraventricular thalamus (PVT) to investigate its impact on arousal and recovery of consciousness in TBI mice. The results showed that optogenetic stimulation of PVT could shorten the latency to arousal and accelerate the recovery of consciousness in these mice. This study identified the PVT as a crucial nucleus involved in maintaining wakefulness.

Applications in Neuronal Cell Protection after Traumatic Brain Injury

Acute brain injury often leads to widespread neuronal cell death, and one of the key factors in this process is the excessive production of reactive oxygen species.[74] The Raf/MEK/ERK and PI3K/AKT pathways are widely recognized as antioxidant stress survival pathways. However, traditional research methods have been limited in their ability to comprehensively understand the temporal dynamics and spatial aspects of these two pathways.

The emergence of optogenetics has provided a solution to this issue. Ong *et al*.[75] conducted cell experiments using optogenetic stimulation on PC12 neurons at different time points to investigate the protective effects of the Raf/MEK/ERK and PI3K/AKT pathways. They found that activating the Raf/ERK pathway before oxidative exposure provided greater protection than the AKT pathway. Furthermore, they discovered that just 15 min of Raf/ERK pathway activation was sufficient to confer protection against oxidative exposure even after a delay of 12 h. After oxidative exposure, the protective effect of the AKT pathway became more prominent than that of the Raf/ERK pathway. The optimal duration of AKT pathway activation for protection was observed at 2 h.

These findings suggest that optogenetics holds great promise in protecting against neuronal cell damage following TBI.

Summary and Outlook

In conclusion, optogenetics has made significant contributions to the understanding of the pathological mechanisms of TBI, disease monitoring, and disorder rehabilitation. Although research in this field is still at the basic experimental level, it has provided valuable insights and new perspectives for exploring therapeutic targets. Optogenetics has emerged as a crucial tool in the study of disease mechanisms, particularly in the field of neurological disorders.

However, the clinical application of optogenetic techniques in treating neurological diseases still faces significant challenges. One of the significant challenges in the clinical application of optogenetic methods is the immune response to viral vectors. Opsins expressed in target brain tissues can also trigger severe immune reactions and may struggle with sustained expression. In addition, there is a risk of viral vector replication in the human brain. Thorough investigation and research are needed to ensure that viral vectors can precisely target the desired genome without causing adverse immune reactions. Future research should focus on developing safer vectors, opsins with long-term expression and low immunogenicity, other efficient nonviral gene delivery methods, and the use of relevant immunosuppressants to enhance the safety and feasibility of these therapeutic approaches. Another crucial concern in optogenetic therapy is the need for invasive surgery to implant optical devices, which carries risks of brain tissue infection and damage. In addition, the weight and size of these implants can significantly hinder patients' daily activities. The light delivered to deep brain tissues may be scattered and absorbed, reducing the effectiveness of optical stimulation. Furthermore, phototoxicity and thermal toxicity from the light can cause tissue damage and adverse outcomes. Future research should focus on developing lighter and safer implantable devices. Safer light delivery methods could significantly enhance the safety and efficacy of optogenetic tools, such as near-infrared light, microwaves, two-photon excitation, and magnetic resonant coupling. Incorporating cooling mechanisms in light delivery devices may reduce thermal toxicity, optimize light transmission efficiency, and decrease tissue exposure time, thus protecting against damage.

Notwithstanding these considerable obstacles, there have been groundbreaking advancements in the clinical application of optogenetics for vision restoration. Sahel *et al*.[76] demonstrated partial visual function restoration in a blind patient by injecting an AAV vector encoding ChrimsonR into the eye and utilizing optogenetic stimulation through engineered goggles to activate genetically modified retinal ganglion cells. Furthermore, the successful application of optogenetic techniques in nonhuman primate models has also been achieved. Stauffer *et al*.[77] selectively and effectively activated dopamine neurons in rhesus macaques. These research breakthroughs instill hope for the clinical application of optogenetics in the treatment of neurological disorders. With the rapid development of optogenetic technology, the application of optogenetics in the clinical treatment of TBI is highly promising and worth anticipating.

Author contributions

Cheng-Hao Lin, Bei-Yao Gao and Shan Jiang conceived the idea. Cheng-Hao Lin and Bei-Yao Gao analysed the data and wrote the initial draft of the paper. Shan Jiang, Rui-Dong Ge, Rui Cui and Wen Han refined the ideas, carried out additional analysed and finalizing this paper. All authors discussed the results and revised the manuscript.

Ethical statement

This review is based solely on previously published studies. No new human or animal studies were conducted by the authors. All data and information used in this review are publicly available and have been properly cited. The original studies were conducted in accordance with the Declaration of Helsinki and were approved by the relevant institutional review boards, as reported by the respective authors.

Data availability statement

Data sharing not applicable to this article as no datasets were generated and/or analyzed during the current study.

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Conflicts of interest

There are no conflicts of interest.

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