Int J Physiol Pathophysiol Pharmacol 2016;8(1):1-8
www.ijppp.org /ISSN:1944-8171/IJPPP0024444

Review Article

Optogenetics for neurodegenerative diseases

Kiara T Vann, Zhi-Gang Xiong

Neuroscience Institute, Morehouse School of Medicine, Atlanta, GA 30310

Received January 19, 2016; Accepted February 22, 2016; Epub April 25, 2016; Published April 30, 2016

Abstract: Neurodegenerative diseases are devastating conditions that lead to progressive degeneration of neurons. Neurodegeneration may result in ataxia, dementia, and muscle atrophies, etc. Despite enormous research efforts that have been made, there is lack of effective therapeutic interventions for most of these diseases. Optogenetics is a recently developed novel technique that combines optics and genetics to modulate the activity of specific neurons. Optogenetics has been implemented in various studies including neuropsychiatric disorders and neurodegenerative diseases. This review focuses on the recent advance in using this technique for the studies of common neurodegenerative diseases.

Keywords: Optogenetics, neurodegenerative diseases, channelrhodopsin, halorhodopsin

Introduction

Optogenetics refers to the combination of optics and genetics to manipulate the activity of individual neurons. It is a novel technique for neuroscience research because of its spatial and temporal precision in controlling neuronal activities. The key element of optogenetics is light-sensitive opsins that either activate or inhibit neurons.

Channelrhodopsin and Halorhodopsin are the two primary light-sensitive opsins used in the majority of optogenetic research. Channelrhodopsins were discovered by Nagel and colleagues in 2002 [1]. They are light-sensitive proteins isolated from the alga *Chlamydomonas reinhardtii*. Nagel et al. demonstrated that Channelrhodopsins-1 (ChR1) and Channelrhodopsins-2 (ChR2) are cation selective channels that allow ion influx when stimulated by blue light [1]. Later on, Boyden and colleagues were able to use a lentiviral vector to express ChR2 in mammalian neurons. When illuminated by blue light, it evokes inward currents, which depolarize the membrane, resulting in firing of action potentials [2, 3]. Halorhodopsin (NpHR) is a light-sensitive chloride pump isolated from *Natronomonas pharanois*. When activated by yellow light, NpHR pumps chloride ions into the cell which hyperpolarizes the membrane and inhibits neural activity [4, 5]. Although the optogenetic technique only has a short history of ~10 years, it has been rapidly and widely used for large number of studies.

Parkinson's disease

Parkinson's disease (PD) is a common neurodegenerative disease of the central nervous system. PD results from the death of dopamine neurons in substantia nigra. Traditional treatments of PD include pharmacological interventions to increase the level of dopamine, and deep brain stimulation (DBS). Because of the heterogeneity of brain tissues where electrodes are placed, it has been challenging to elucidate the relevant target cell types or underlying mechanisms of DBS. Pharmacological interventions, on the other hand, have various limitations and side effects.

In 2009, Gradinaru and colleagues used optogenetics and solid-state optics to systematically drive or inhibit an array of distinct circuit elements in freely moving parkinsonian rodents and found that therapeutic effects within the subthalamic nucleus can be accounted for by direct selective stimulation of afferent axons projecting to this region [6]. In addition to providing insight into DBS mechanisms, these results demonstrated an optical approach for

dissection of disease circuitry and provided a new way for systematic deconstruction of disease circuits by selectively controlling individual components.

In addition to DBS and pharmacological intervention, previous studies have suggested that cell replacement could be a viable therapeutic option for PD. The evidence of behavioral recovery after transplantation of human pluripotent stem cell-derived neural cells in animal models of PD has been provided [7-9]. However, little is known about the mechanisms underlying graft function.

In a recent study by Steinbeck and colleagues, optogenetics was utilized to investigate graft function and graft to host connectivity [10]. The technique was applied to modulate the electrophysiological and neurochemical properties of mesencephalic dopaminergic (mesDA) neurons derived from human embryonic stem cells (hESCs) [10]. To examine the functionality of mesDA neurons transplanted in lesioned striatum, undifferentiated hESCs were transduced to express halorhodopsin eNpHR3.0-EYFP (called HALO) or EYFP alone under the control of the human synapsin promoter [11-13]. It was demonstrated that deactivation of HALO-expressing grafts by light produced motor deficits. Pre-treating animals with apomorphine, an agonist for D1 and D2 dopamine receptors, did not result in the return of motor deficits when HALO-expressing grafts became deactivated. Electrophysiological recordings from acute brain slices demonstrated that stimulation of the corpus callosum evoked dopamine release from the graft and excitatory postsynaptic potentials (EPSPs) in striatal GABA neurons [10]. However, optogenetic silencing resulted in significant reduction in evoked EPSP. This result suggests that grafted neurons strengthen EPSP response of host striatal GABA neurons through an activation of D1 receptors. The findings also suggest the importance of graft neuronal activity and connectivity in behavioral recovery of PD.

Huntington's disease

Huntington's Disease (HD) is a genetic neurodegenerative disorder that affects muscle coordination with mental decline at late stages. HD is caused by an autosomal dominant mutation in a gene called Huntingtin. As the disease progresses uncoordinated body movements begin to occur and declines in mental abilities become apparent.

In mouse models of HD, studies have shown that spontaneous inhibitory synaptic activity is enhanced in a subpopulation of medium-sized spiny neurons (MSNs), which dampens striatal output. The sources of increased inhibition were, however, unclear. In a recent study, Cepeda and colleagues examined the potential source(s) of increased inhibition using electrophysiological and optogenetic methods to assess feedback and feedforward inhibition in two transgenic mouse models of HD [14].

Channelrhodopsin-2 and EYFP were inserted into a double-floxed inverted open reading frame viral vector (AAV2-DIO-ChR2-EYFP) to selectively activate GABAergic interneurons and evaluate the influence on GABA synaptic activity in MSNs [14]. Single and dual patch-clamp recordings were performed in MSNs of striatal slices and two types of GABAergic interneurons were studied: the fast-spiking (FS) and the persistent low-threshold spiking (PLTS) interneurons. They observed selective alterations in GABA synaptic activity in MSNs under the control of D1 (direct pathway) or D2 (indirect pathway) promoters [15-18]. These findings demonstrated that in HD multiple sources contribute to increased GABA activity on MSNs of the indirect pathway [14]. Most of the contribution comes from feedforward inhibition from FS and PLTS interneurons. PLTS interneurons are responsible for the increased GABAergic spontaneous synaptic events while activated FS interneurons are the source of larger GABA-mediated synaptic responses [14]. PLTS interneurons can release nitric oxide (NO), neuropeptide Y (NPY) and somatostatin (SOM) which could have neuroprotective effects [19-21]. The selective inhibition of striatal PLTS and FS interneurons could improve HD behavioral phenotype. These findings suggest that selectively controlling PLTS and FS interneurons could be beneficial in improving behavior of HD patients.

Epilepsy

Epilepsy is a common neurological disorder characterized by epileptic seizures. Currently available antiepileptic drugs have a limited efficacy, and their long term use is limited due to

the adverse effects, withdrawal symptoms, and deleterious interactions with other drugs, etc. Furthermore, some of the available antiepileptic drugs may even potentiate certain type of seizures. Therefore, new therapeutic intervention is highly desirable [22].

In 2009, Tonnesen and colleagues explored the possibility of using optogenetics for the treatment of epileptic seizures. They used lentiviral vector to target NpHR specifically to the principal neurons of the hippocampus in mice under the control of CaMKIIα promoter [23]. They showed that light-induced NpHR activity hyperpolarizes the principal neurons of hippocampus and inhibited epileptiform activity. In this study, it was established that epileptiform activity can be directly inhibited by using hyperpolarizing actuators [23].

In 2013, Paz and colleagues were able to express enhanced halorhodopsin (eNpHR3.0) in neurons of the ventrobasal thalamus [24, 25]. In addition, they were able to design closed-loop devices that can stop the seizures in real-time light stimulation. Subsequently, Sukhotinsky et al. employed adeno-associated virus vector (AAV) to target eNpHR3.0 to hippocampal pyramidal cells and demonstrated that constant and sporadic illumination hindered electrographic and behavioral onset of seizure activity [26].

A very recent study by Soper and colleagues also employed the optogenetic technique to examine the anticonvulsant effect of optical stimulation of the deep/intermediate layers of the superior colliculus (DLSC) [27]. In their experimentation, rAAV5-hSyn-ChR2 (H134R)-mCherry was microinjected into the DLSC. They demonstrated that activation of DLSC can exert broad-spectrum anticonvulsant actions, attenuating seizures originating in diverse and distal brain networks. For example, stimulation of DLSC can suppress the behavioral and electrographic seizures activity in the pentylenetetrazole induced forebrain/brainstem seizures and Area Tempestas induced forebrain/complex partial seizures. In addition, DLSC activation also attenuated thalamocortical/absence seizures evoked by gamma butyrolactone, or brainstem seizures induced by acoustic stimulation of genetically epilepsy prone rates [27]. Their findings suggested that selective, temporally-controlled activation of DLSC is a promising strategy for the therapeutic intervention of epilepsy [27].

Thus, optogenetics may be an ideal approach for controlling neurons to treat epilepsy with real time response.

Alzheimer disease

Aggregation of amyloid β peptides is a hallmark pathological change in the brains of patients with Alzheimer disease (AD) [28]. However, the mechanisms for the secretion and aggregation of amyloid β peptides remained elusive. Previous studies using electrical or pharmacological stimulations have shown that Aβ secretion from neurons is activity dependent [29-31]. However, the exact pathways involved were not clear. In a recent study by Yamamoto and colleagues, optogenetics was adopted to examine the selective activation of a specific neuronal pathway in APP transgenic mice to observe the causative role between synaptic activation and Aβ pathology [32]. Stabilized step-function opsin (SSFO), a channelrhodopsin designed to elicit a long-lasting neuronal hyperexcitability, was expressed in the hippocampal perforant pathway of APP transgenic mice. Specifically, SSFO-EYFP in adeno-associated virus vector driven by a CAMKIIα promoter was unilaterally transduced into the lateral entorhinal cortex to selectively stimulate the cortical projection neurons through the perforant pathway [32]. In vivo microdialysis revealed a ~24% increase of Aβ42 level in the hippocampal interstitial fluid immediately after acute light activation. Mice with chronic optogenetic stimulation for 5 months had a dramatic 2.5-fold increase of Aβ deposits [32]. These findings suggest a connection between hyperactivity of specific projection pathway and augmentation in Aβ deposition. This study also provided the foundation for further research using optogenetics for chronic stimulation in animal models of neurodegenerative disorders.

Stroke

Stroke is caused by poor circulation to the brain resulting in injury of brain cells. It is a leading cause of death and long-term disabilities. Current treatment for stroke is limited to the use of tPA which has limited success and potential side effect of intracerebral hemorrhage. Thus, searching for new therapeutic

intervention for stroke treatment or recovery has been a major challenge.

In a recent study by Cheng and colleagues, optogenetics was used to promote stroke recovery by selectively increasing neuronal activity in the ipsilesional primary motor cortex (iM1) poststroke [33, 34]. Stroke recovery was examined in ChR2-expressing transgenic mice under Thy1 promoter. In their study, they observed the effects on functional recovery following optic stimulations [34]. Light-stimulated stroke mice had improved performance on rotating beam test and stimulus-induced cerebral blood flow, which indicates improved recovery [33]. It was shown that increased excitability in the iM1 was beneficial and fostered the poststroke recovery. This study provided strong evidence that optogenetics can be used to promote stroke recovery and that stimulating neurons in the stroke hemisphere is necessary to improve the recovery.

Sensory system degeneration

Retinopathies: Retinopathies are noninflammatory diseases of the retina. Damage to the retina results in vision impairments and in some cases even blindness. Retinopathies have various causes. Common retinopathies include macular degeneration and retinitis pigmentosa. The macula is responsible for sharp, center vision. Age-related macular degeneration (AMD) is a leading cause of vision loss in people over 50 [35]. Retinitis pigmentosa (RP) is a group of rare, genetic disorders that involve deterioration of cells in the retina [36]. RP symptoms include night blindness and loss of peripheral vision. Current treatments for retinopathies include dugs of anti-vascular endothelial growth factors (VEGF), gene therapy, stem cells and visual assistive devices [37]. However, these methods have limited success and cannot restore visual loss of natural images.

In 2006, Bi and colleagues investigated the feasibility of using ChR2 to restore light sensitivity to the retinas that have undergone rod and cone degeneration [38]. They transfected *rd1* mouse retinas with ChR2. The *rd1* mouse is a well-characterized animal model of retinitis pigmentosa caused by the mutation of Pde6b gene. They showed that long-term expression of ChR2 can be achieved in rodent inner retinal neurons in vivo and that these inner retinal neurons can express a sufficient number of functional ChR2 channels to produce robust membrane depolarization or action potential firing without an exogenous supply of all-trans retinal. Furthermore, they demonstrated that the expression of ChR2 in a photoreceptor-deficient mouse model not only enables retinal ganglion cells to encode light signals but also restores visually evoked responses in the visual cortex.

Later on, similar results were observed in a number of studies by Tomita and colleagues, who were able to restore visual response in aged dystrophic RCS rats and functional vision in genetically blind rats using AAV-mediated channelopsin-2 gene transfer to retinal ganglion cells [39-41]. However, in a study performed by Thyagarajan and colleagues, the expression of ChR2 in retinal ganglion cells failed to rescue vision [43]. Several studies have shown that activation of channelrhodopsin-2 targeted specifically to ON bipolar cells can also restore visual function in mice with retinal degeneration [42, 44].

In 2010, Busskamp et al showed that expression of archaebacterial halorhodopsin in light-insensitive cones can substitute for the native phototransduction cascade and restore light sensitivity in mouse models of retinitis pigmentosa [45]. In this case, halorhodopsin is a better option than ChR2 due to the fact that cones are usually depolarized in the dark and hyperpolarized in response to light.

Nirenberg and colleagues stimulated blind mouse retinas expressing ChR2 with natural images processed by computational model of retinal encoding [46]. In this study, they generated a prosthetic system that incorporates the code, which dramatically increased the system's capabilities. Furthermore, they showed that, using 9,800 optogenetically stimulated ganglion cell responses, the combined effect of using the code and high-resolution stimulation is able to bring prosthetic capabilities up to the level of normal or near-normal image representation.

In a recent study by van Wyk and colleagues, a new optogenetic approach was employed by using next-generation optogenetic tool, OptomGluR6, to target ON bipolar cells, which overcomes limitations from traditional optogenetic approach such as low light sensitivity and phys-

Table 1. Optogenetic studies of neurodegenerative diseases

Neurodegenerative Disorders	Optogenetic Actuators	Parameter(s) studied	References
Alzheimer's Disease	Stabilized Step-Function Opsins	Amyloid β peptide release	[32]
Stroke	Channedlrhodopsin-2	Functional recovery	[33, 34]
Epilepsy	Halorhodopsin	Seizure suppression	[23-27]
Parkinson's Disease	Halorhodopsin	Graft function and graft to host connectivity	[6, 10]
Huntington's Disease	Channelrhodopsin-2	Sources of increased inhibition	[14]
Retinopathies	Channelrhodopsin-2	Vision restore	[38-40, 42, 43, 45-47]
Auditory Dysfunction	Channelrhodopsin-2	Cochlear excitation	[49, 51-53]
	Chronos		[49]

iological compatibility issues [47]. They showed that Opto-mGluR6, a chimeric protein consisting of the intracellular domains of the ON-bipolar cell-specific metabotropic glutamate receptor mGluR6 and the light-sensing domains of melanopsin, reliably recovers vision at the retinal, cortical, and behavioral levels under moderate daylight illumination.

Hearing loss

Hearing loss or anacusis is a partial or total inability to hear. Hearing impairments can also affect the ability to learn language as well as cause work-related difficulties. Cochlear implants are the most successful neuroprothesis which can deliver profound auditory gains to individuals with severe to profound hearing loss. An auditory brainstem implant (ABI) is an alternative to cochlear implants; it provide hearing sensations to patients who are not eligible candidates for cochlear implants due to anatomic concerns [48]. However, ABI performance is limited by its dependence on electrical stimulation with its associated channel cross-talk and current spread to non-auditory neurons. The optogenetic technology could serve as new generation ABI that ameliorates limitations fundamental to electrical stimulation [49].

In 2013, Shimano and colleagues inserted the AAV-mediated expression of channelrhodopsin-2 and halorhodopsin in brainstem neurons mediating auditory signaling: the dorsal cochlear nucleus neurons (DCN) [50]. Their results indicated that expression and activation of rhodopsin within neurons involved in auditory processing does not appear to have deleterious effects on hearing even after 18 months following the expression. In addition, virally targeted rhodopsins may be useful as tract tracers to delineate as well as modulate the activity of auditory pathways.

Later on in 2014, Hernandez and colleagues used optogenetics to stimulate spiral ganglion neurons (SGNs) with low intensity blue light, using transgenic mice with neuronal expression of channelrhodopsin 2 or virus-mediated expression of the ChR2-variant CatCh [51, 52]. ChR2-expressing SGNs were stimulated with micro-light emitting diodes (μLEDs) and fiber-coupled lasers through a small artificial opening (cochleostomy) or the round window. The optogenetic auditory brainstem responses were assayed by scalp recordings of light-evoked potentials or by microelectrode recordings from the auditory pathway and compared them with acoustic and electrical stimulation. Stimulation of SGNs activated the auditory pathway, as demonstrated by recordings of single neuron and neuronal population responses. Furthermore, optogenetic stimulation of SGNs restored auditory activity in deaf mice [51, 52].

Recently, Darrow and colleagues investigated whether optical activation of the cochlear nucleus (CN) can evoke responses in neurons at higher centers of the auditory pathway [53]. Channelrhodopsin-2 was expressed in the mouse CN using viral-mediated gene transfer. Optical stimulation evoked excitatory responses throughout the tonotopic axis of the central nucleus of the inferior colliculus (IC) and auditory cortex. Optical stimulation also evoked an auditory brainstem response.

Previous studies of the kinetics of ChR2 and its variants [2, 54] indicated that ChR2 could be too slow for optimal function in the auditory system. In a recent study by Hight and colleagues, they addressed the limitations of ChR2 by employing Chronos, a recently devel-

oped opsin with faster kinetic properties [55], to compare the temporal characteristics of ChR2 and Chronos in a translational murine ABI model [49]. Their findings revealed that Chronos has the capacity to drive the auditory system at greater stimulation rates than ChR2 and that it may be a better option for controlling auditory pathways.

Conclusion

Steady research efforts are being made to treat neurodegenerative diseases. Increasing evidence indicates the potential of optogenetics as a promising therapeutic approach (**Table 1**). However; the current optogenetic approaches have a few limitations. For example, optogenetic technique requires the delivery of photons into the brain, which is achieved invasively via implantation of optic fiber through the skull into specific brain areas. This drawback may restrict animal's motility, confounding the interpretation of behavioral readouts. The optic fiber itself is susceptible to damage caused by activity of the animal, and its implantation may results in tissue damage in the brain regions of interest. Another consideration when using optogenetics is the possibility that the light evokes modulation of fibers of passage and not acting exclusively on the axons or terminals of interest. The approach may possibly cause light-induced or heat-related damage to the tissue. The development of infrared sensitive opsins has the possibility of reducing light-induced tissue damage and delivering photons into targeted brain areas without the need for invasive methods. In addition, recently developed giant magentoresistive (GMR) biosensors and nanoparticles controlled by radio waves provide alternative non-invasive approaches. Although a short history, optogenetics has proved itself as a promising alternative approach to traditional therapeutic treatments.

Acknowledgements

The work in our laboratory is supported by NIH R01NS66027, U54NS083932, and NIMHDS21-MD000101.

Address correspondence to: Zhi-Gang Xiong, Neuroscience Institute, Morehouse School of Medicine, 720 Westview Drive Southwest, Atlanta, GA 30310. Tel: 404-752-8683; E-mail: zxiong@msm.edu

References

[1] Nagel G, Ollig D, Fuhrmann M, Kateriya S, Musti AM, Bamberg E, Hegemann P. Channelrhodopsin-1: a light-gated proton channel in green algae. Science 2002; 296: 2395-2398.

[2] Boyden ES, Zhang F, Bamberg E, Nagel G and Deisseroth K. Millisecond-timescale, genetically targeted optical control of neural activity. Nat Neurosci 2005; 8: 1263-1268.

[3] Ishizuka T, Kakuda M, Araki R and Yawo H. Kinetic evaluation of photosensitivity in genetically engineered neurons expressing green algae light-gated channels. Neurosci Res 2006; 54: 85-94.

[4] Lanyi JK and Oesterhelt D. Identification of the retinal-binding protein in halorhodopsin. J Biol Chem 1982; 257: 2674-2677.

[5] Schobert B and Lanyi JK. Halorhodopsin is a light-driven chloride pump. J Biol Chem 1982; 257: 10306-10313.

[6] Gradinaru V, Mogri M, Thompson KR, Henderson JM and Deisseroth K. Optical deconstruction of parkinsonian neural circuitry. Science 2009; 324: 354-359.

[7] Kim JH, Auerbach JM, Rodriguez-Gomez JA, Velasco I, Gavin D, Lumelsky N, Lee SH, Nguyen J, Sanchez-Pernaute R, Bankiewicz K and McKay R. Dopamine neurons derived from embryonic stem cells function in an animal model of Parkinson's disease. Nature 2002; 418: 50-56.

[8] Brederlau A, Correia AS, Anisimov SV, Elmi M, Paul G, Roybon L, Morizane A, Bergquist F, Riebe I, Nannmark U, Carta M, Hanse E, Takahashi J, Sasai Y, Funa K, Brundin P, Eriksson PS and Li JY. Transplantation of human embryonic stem cell-derived cells to a rat model of Parkinson's disease: effect of in vitro differentiation on graft survival and teratoma formation. Stem Cells 2006; 24: 1433-1440.

[9] Ben-Hur T, Idelson M, Khaner H, Pera M, Reinhartz E, Itzik A and Reubinoff BE. Transplantation of human embryonic stem cell-derived neural progenitors improves behavioral deficit in Parkinsonian rats. Stem Cells 2004; 22: 1246-1255.

[10] Steinbeck JA, Choi SJ, Mrejeru A, Ganat Y, Deisseroth K, Sulzer D, Mosharov EV and Studer L. Optogenetics enables functional analysis of human embryonic stem cell-derived grafts in a Parkinson's disease model. Nat Biotechnol 2015; 33: 204-209.

[11] Kriks S, Shim JW, Piao J, Ganat YM, Wakeman DR, Xie Z, Carrillo-Reid L, Auyeung G, Antonacci C, Buch A, Yang L, Beal MF, Surmeier DJ, Kordower JH, Tabar V and Studer L. Dopamine neurons derived from human ES cells efficient-

ly engraft in animal models of Parkinson's disease. Nature 2011; 480: 547-551.
[12] Kirkeby A, Grealish S, Wolf DA, Nelander J, Wood J, Lundblad M, Lindvall O and Parmar M. Generation of regionally specified neural progenitors and functional neurons from human embryonic stem cells under defined conditions. Cell Rep 2012; 1: 703-714.
[13] Roy NS, Cleren C, Singh SK, Yang L, Beal MF and Goldman SA. Functional engraftment of human ES cell-derived dopaminergic neurons enriched by coculture with telomerase-immortalized midbrain astrocytes. Nat Med 2006; 12: 1259-1268.
[14] Cepeda C, Galvan L, Holley SM, Rao SP, Andre VM, Botelho EP, Chen JY, Watson JB, Deisseroth K and Levine MS. Multiple Sources of Striatal Inhibition Are Differentially Affected in Huntingtons Disease Mouse Models. J Neurosci 2013; 33: 7393-7406.
[15] Cepeda C, Andre VM, Yamazaki I, Wu N, Kleiman-Weiner M and Levine MS. Differential electrophysiological properties of dopamine D1 and D2 receptor-containing striatal medium-sized spiny neurons. Eur J Neurosci 2008; 27: 671-682.
[16] Andre VM, Cepeda C, Fisher YE, Huynh M, Bardakjian N, Singh S, Yang XW and Levine MS. Differential electrophysiological changes in striatal output neurons in Huntington's disease. J Neurosci 2011; 31: 1170-1182.
[17] Andre VM, Fisher YE and Levine MS. Altered Balance of Activity in the Striatal Direct and Indirect Pathways in Mouse Models of Huntington's Disease. Front Syst Neurosci 2011; 5: 46.
[18] Andre VM, Cepeda C, Fisher YE, Huynh M, Bardakjian N, Singh S, Yang XW and Levine MS. Differential electrophysiological changes in striatal output neurons in Huntington's disease. J Neurosci 2011; 31: 1170-1182.
[19] Kawaguchi Y, Wilson CJ, Augood SJ and Emson PC. Striatal interneurones: chemical, physiological and morphological characterization. Trends Neurosci 1995; 18: 527-535.
[20] Deckel AW. Nitric oxide and nitric oxide synthase in Huntington's disease. J Neurosci Res 2001; 64: 99-107.
[21] Galarraga E, Vilchis C, Tkatch T, Salgado H, Tecuapetla F, Perez-Rosello T, Perez-Garci E, Hernandez-Echeagaray E, Surmeier DJ and Bargas J. Somatostatinergic modulation of firing pattern and calcium-activated potassium currents in medium spiny neostriatal neurons. Neuroscience 2007; 146: 537-554.
[22] Wahab A, Albus K, Gabriel S and Heinemann U. In search of models of pharmacoresistant epilepsy. Epilepsia 2010; 51 Suppl 3: 154-159.
[23] Tonnesen J, Sorensen AT, Deisseroth K, Lundberg C and Kokaia M. Optogenetic control of epileptiform activity. Proc Natl Acad Sci U S A 2009; 106: 12162-12167.
[24] Paz JT, Davidson TJ, Frechette ES, Delord B, Parada I, Peng K, Deisseroth K and Huguenard JR. Closed-loop optogenetic control of thalamus as a tool for interrupting seizures after cortical injury. Nat Neurosci 2013; 16: 64-70.
[25] Ji ZG and Wang H. Optogenetic control of astrocytes: Is it possible to treat astrocyte-related epilepsy? Brain Research Bulletin 2015; 110: 20-25.
[26] Sukhotinsky I, Chan AM, Ahmed OJ, Rao VR, Gradinaru V, Ramakrishnan C, Deisseroth K, Majewska AK and Cash SS. Optogenetic delay of status epilepticus onset in an in vivo rodent epilepsy model. PLoS One 2013; 8: e62013
[27] Soper C, Wicker E, Kulick CV, N'Gouemo P and Forcelli PA. Optogenetic activation of superior colliculus neurons suppresses seizures originating in diverse brain networks. Neurobiol Dis 2016; 87: 102-115.
[28] Selkoe D, Mandelkow E and Holtzman D. Deciphering Alzheimer disease. Cold Spring Harb Perspect Med 2012; 2: a011460
[29] Kamenetz F, Tomita T, Hsieh H, Seabrook G, Borchelt D, Iwatsubo T, Sisodia S and Malinow R. APP Processing and Synaptic Function. Neuron 37: 925-937.
[30] Cirrito JR, Kang JE, Lee J, Stewart FR, Verges DK, Silverio LM, Bu G, Mennerick S and Holtzman DM. Endocytosis is required for synaptic activity-dependent release of amyloid-beta in vivo. Neuron 2008; 58: 42-51.
[31] Cirrito JR, Yamada KA, Finn MB, Sloviter RS, Bales KR, May PC, Schoepp DD, Paul SM, Mennerick S and Holtzman DM. Synaptic activity regulates interstitial fluid amyloid-beta levels in vivo. Neuron 2005; 48: 913-922.
[32] Yamamoto K, Tanei Z, Hashimoto T, Wakabayashi T, Okuno H, Naka Y, Yizhar O, Fenno LE, Fukayama M, Bito H, Cirrito JR, Holtzman DM, Deisseroth K and Iwatsubo T. Chronic optogenetic activation augments abeta pathology in a mouse model of Alzheimer disease. Cell Rep 2015; 11: 859-865.
[33] Cheng MY, Wang EH, Woodson WJ, Wang S, Sun G, Lee AG, Arac A, Fenno LE, Deisseroth K and Steinberg GK. Optogenetic neuronal stimulation promotes functional recovery after stroke. Proc Natl Acad Sci U S A 2014; 111: 12913-12918.
[34] Cheng MY, Wang EH and Steinberg GK. Optogenetic Approaches to Study Stroke Recovery. ACS Chem Neurosci 2014; 5: 1144-1145.
[35] Congdon N, O'Colmain B, Klaver CC, Klein R, Muñoz B, Friedman DS, Kempen J, Taylor HR, Mitchell P; Eye Diseases Prevalence Research Group. CAuses and prevalence of visual impairment among adults in the united states. Arch Ophthalmol 2004; 122: 477-485.

[36] Hamel C. Retinitis pigmentosa. Orphanet J Rare Dis 2006; 1: 40-40.
[37] Agarwal A, Rhoades WR, Hanout M, Soliman MK, Sarwar S, Sadiq MA, Sepah YJ, Do DV and Nguyen QD. Management of neovascular age-related macular degeneration: current state-of-the-art care for optimizing visual outcomes and therapies in development. Clin Ophthalmol 2015; 9: 1001-1015.
[38] Bi A, Cui J, Ma YP, Olshevskaya E, Pu M, Dizhoor AM and Pan ZH. Ectopic expression of a microbial-type rhodopsin restores visual responses in mice with photoreceptor degeneration. Neuron 2006; 50: 23-33.
[39] Tomita H, Sugano E, Yawo H, Ishizuka T, Isago H, Narikawa S, Kugler S and Tamai M. Restoration of visual response in aged dystrophic RCS rats using AAV-mediated channelopsin-2 gene transfer. Invest Ophthalmol Vis Sci 2007; 48: 3821-3826.
[40] Tomita H, Sugano E, Isago H, Hiroi T, Wang Z, Ohta E and Tamai M. Channelrhodopsin-2 gene transduced into retinal ganglion cells restores functional vision in genetically blind rats. Exp Eye Res 2010; 90: 429-436.
[41] Tomita H, Sugano E, Fukazawa Y, Isago H, Sugiyama Y, Hiroi T, Ishizuka T, Mushiake H, Kato M, Hirabayashi M, Shigemoto R, Yawo H and Tamai M. Visual properties of transgenic rats harboring the channelrhodopsin-2 gene regulated by the thy-1.2 promoter. PLoS One 2009; 4: e7679.
[42] Doroudchi MM, Greenberg KP, Liu J, Silka KA, Boyden ES, Lockridge JA, Arman AC, Janani R, Boye SE, Boye SL, Gordon GM, Matteo BC, Sampath AP, Hauswirth WW and Horsager A. Virally delivered channelrhodopsin-2 safely and effectively restores visual function in multiple mouse models of blindness. Mol Ther 2011; 19: 1220-1229.
[43] Thyagarajan S, van WM, Lehmann K, Lowel S, Feng G and Wassle H. Visual function in mice with photoreceptor degeneration and transgenic expression of channelrhodopsin 2 in ganglion cells. J Neurosci 2010; 30: 8745-8758.
[44] Lagali PS, Balya D, Awatramani GB, Munch TA, Kim DS, Busskamp V, Cepko CL and Roska B. Light-activated channels targeted to ON bipolar cells restore visual function in retinal degeneration. Nat Neurosci 2008; 11: 667-675.
[45] Busskamp V, Duebel J, Balya D, Fradot M, Viney TJ, Siegert S, Groner AC, Cabuy E, Forster V, Seeliger M, Biel M, Humphries P, Paques M, Mohand-Said S, Trono D, Deisseroth K, Sahel JA, Picaud S and Roska B. Genetic reactivation of cone photoreceptors restores visual responses in retinitis pigmentosa. Science 2010; 329: 413-417.
[46] Nirenberg S and Pandarinath C. Retinal prosthetic strategy with the capacity to restore normal vision. Proc Natl Acad Sci U S A 2012; 109: 15012-15017.
[47] van WM, Pielecka-Fortuna J, Lowel S and Kleinlogel S. Restoring the ON Switch in Blind Retinas: Opto-mGluR6, a Next-Generation, Cell-Tailored Optogenetic Tool. PLoS Biol 2015; 13: e1002143
[48] Colletti V, Carner M, Miorelli V, Guida M, Colletti L and Fiorino F. Auditory Brainstem Implant (ABI): New Frontiers in Adults and Children. Otolaryngol Head Neck Surg 2005; 133: 126-138.
[49] Hight AE, Kozin ED, Darrow K, Lehmann A, Boyden E, Brown MC and Lee DJ. Superior temporal resolution of Chronos versus channelrhodopsin-2 in an optogenetic model of the auditory brainstem implant. Hear Res 2015; 322: 235-241.
[50] Shimano T, Fyk-Kolodziej B, Mirza N, Asako M, Tomoda K, Bledsoe S, Pan ZH, Molitor S and Holt AG. Assessment of the AAV-mediated expression of channelrhodopsin-2 and halorhodopsin in brainstem neurons mediating auditory signaling. Brain Res 2013; 1511: 138-152.
[51] Hernandez VH, Gehrt A, Jing Z, Hoch G, Jeschke M, Strenzke N and Moser T. Optogenetic stimulation of the auditory nerve. J Vis Exp 2014; e52069.
[52] Hernandez VH, Gehrt A, Reuter K, Jing Z, Jeschke M, Mendoza SA, Hoch G, Bartels M, Vogt G, Garnham CW, Yawo H, Fukazawa Y, Augustine GJ, Bamberg E, Kugler S, Salditt T, de HL, Strenzke N and Moser T. Optogenetic stimulation of the auditory pathway. J Clin Invest 2014; 124: 1114-1129.
[53] Darrow KN, Slama MC, Kozin ED, Owoc M, Hancock K, Kempfle J, Edge A, Lacour S, Boyden E, Polley D, Brown MC and Lee DJ. Optogenetic stimulation of the cochlear nucleus using channelrhodopsin-2 evokes activity in the central auditory pathways. Brain Res 2015; 1599: 44-56.
[54] Zhang F, Wang LP, Boyden ES and Deisseroth K. Channelrhodopsin-2 and optical control of excitable cells. Nat Methods 2006; 3: 785-792.
[55] Klapoetke NC, Murata Y, Kim SS, Pulver SR, Birdsey-Benson A, Cho YK, Morimoto TK, Chuong AS, Carpenter EJ, Tian Z, Wang J, Xie Y, Yan Z, Zhang Y, Chow BY, Surek B, Melkonian M, Jayaraman V, Constantine-Paton M, Wong GK and Boyden ES. Independent optical excitation of distinct neural populations. Nat Methods 2014; 11: 338-346.