Life Sciences

Volume 336, 1 January 2024, 122334

Review article

A comprehensive review on therapeutic potentials of photobiomodulation for neurodegenerative disorders

Pooja Ramakrishnan [a 1], Aradhana Joshi [a], Mohamed Fazil [a b], Pankaj Yadav [a 2]

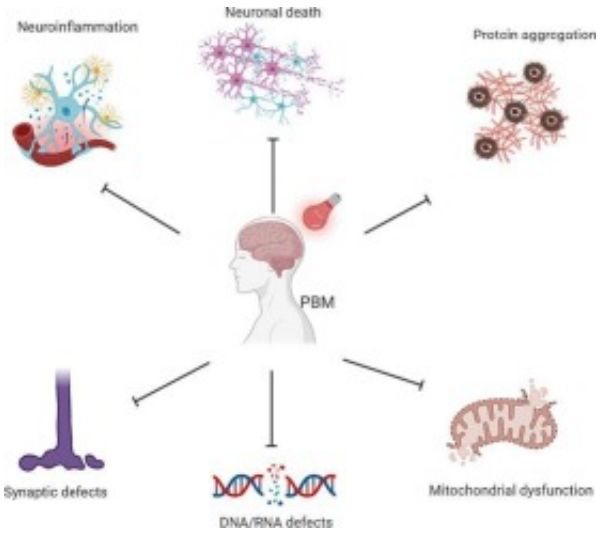
https://doi.org/10.1016/j.lfs.2023.122334

Abstract

A series of experimental trials over the past two centuries has put forth Photobiomodulation (PBM) as a treatment modality that utilizes colored lights for various conditions. While in its cradle, PBM was used for treating simple conditions such as burns and wounds, advancements in recent years have extended the use of PBM for treating complex neurodegenerative diseases (NDDs). PBM has exhibited the potential to curb several symptoms and signs associated with NDDs. While several of the currently used therapeutics cause adverse side effects alongside being highly invasive, PBM on the contrary, seems to be broad-acting, less toxic, and non-invasive. Despite being projected as an ideal therapeutic for NDDs, PBM still isn't considered a mainstream treatment modality due to some of the challenges and knowledge gaps associated with it. Here, we review the advantages of PBM summarized above with an emphasis on the common

mechanisms that underlie major NDDs and how PBM helps tackle them. We also discuss important questions such as whether PBM should be considered a mainstay treatment modality for these conditions and if PBM's properties can be harnessed to develop prophylactic therapies for high-risk individuals and also highlight important animal studies that underscore the importance of PBM and the challenges associated with it. Overall, this review is intended to bring the major advances made in the field to the spotlight alongside addressing the practicalities and caveats to develop PBM as a major therapeutic for NDDs.

Graphical abstract



Download: Download high-res image (46KB)

Download: Download full-size image

Introduction

Neurodegenerative disorders (NDDs) are progressive, age-related disorders that are usually debilitating in nature [1]. Due to the phenomenal increase in average life expectancy, the aging population has grown substantially. Most older individuals suffer from at least one chronic condition most of which are NDDs [[2], [3], [4]]. By 2050, the number of older individuals is expected to almost double which means the global burden of NDDs is bound to increase [5]. In general, treating NDDs is complex due to the presence of the blood-brain barrier (BBB; henceforth), the blood-cerebrospinal fluid

barrier in the central nervous system (CNS; [6]). Moreover, the current therapeutic approaches for NDDs have several associated disadvantages, which impact their efficacy and patient prognosis [7]. One of the major disadvantages of current therapies is the lack of a definitive treatment that can either halt or reverse the progression of NDDs [8]. Available therapeutics primarily focus on managing the symptomatology of the diseases [9]. An exemplification of this is that the medications used to treat Alzheimer's disease (AD), mostly aim at improving cognitive function and slowing down the decline in memory and thinking skills [10]. However, these medications do not address the underlying causes of the disease and cannot stop or reverse its progression [9]. Furthermore, the current therapeutic options for NDDs often manifest significant side effects and safety concerns [11]. For instance, some medications used to treat NDDs are seen to cause severe side effects such as dizziness, seizures, Stevens-Johnson syndrome, and toxicity [11]. NDDs are complex and multifactorial [12], due to which the development of a single treatment that can target all these factors and provide a cure remains a challenge. These disadvantages highlight the limitations of current therapeutic approaches for NDDs and emphasize the need for more effective and targeted treatment options to address the complex pathogenesis of these diseases. Photobiomodulation (PBM) is an approach that harnesses the therapeutic properties of various wavelengths of visible light and has emerged as a potential treatment option for NDDs [13]. The history of PBM as a potential treatment for NDDs can be traced back to its early use in skin diseases and nerve injuries [14]. However, progress in this field helped scientists discover that photobiomodulation could also help in treating NDDs.

Early studies on PBM and its potential use in NDDs focused on its effects in regulating oxidative stress, inflammation, apoptosis, and autophagy [14]. As the understanding of PBM grew, the capability of PBM conferring neuroprotection in experimental models of various NDDs was targeted and established. For instance, studies using animal models of AD and Parkinson's disease (PD) have shown that PBM uses wavelengths ranging from 630 nm to 1100 nm (Red to Near-infrared (NIR) region) lights to ameliorate neuroinflammation, promote neuronal survival and regeneration, improve cognitive function and motor symptoms and enhance brain metabolism and blood flow [[15], [16], [17]]. Furthermore, PBM has been proven greatly effective in alleviating symptoms in genetic models of dementia [14]. Additionally, in clinical studies involving humans, PBM has been reported to be effective against hyperalgesic syndromes such as oral mucositis, carpal tunnel syndrome, neuropathic pain, etc. [[18], [19], [20]]. These positive effects of

PBM make it a potentially ideal treatment option for NDDs. In this review, apart from summarizing the advantages of PBM, we emphasize the common mechanisms that underlie major neurological conditions and examine how PBM is perceived by the human body and subsequently how PBM impacts physiological functions to tackle the NDD hallmarks, signaling pathways, and effector molecules. We also posit our hypothesis that PBM could be developed as a prophylactic therapy for NDDs and address important questions such as whether PBM should be considered a mainstay treatment modality for these conditions and if PBM's properties can be harnessed to develop prophylactic therapies for high-risk individuals. In addition to this, here we critically review some important animal studies revealing the major advances, practicalities, caveats, and challenges associated with PBM that hinder the use of PBM as a major therapeutic for neurological conditions.

Section snippets

Transcranial delivery

Red and NIR light have deep penetration abilities and therefore they pass through the skull and into the cortical surfaces of the brain [21]. PBM is applied non-invasively to the brain trans-cranially [21]. But before reaching the brain, much of the delivered light would get scattered and a very minimal dose would reach the neurons. This is one of the major limitations that prevent the use of PBM as a standard therapeutic technique for neurodegenerative disorders [21]. Further, 830 nm NIR light …

Perceptions of PBM

For the physiological functioning of light, photoreception must be first conferred by a

specific molecule through which cells in the body detect and respond to light [39]. In biological tissues, different wavelengths of light are absorbed, scattered, and reflected in varying degrees [40]. Molecules that possess the ability to absorb specific wavelengths of light are called chromophores [41] and biological tissues possess a range of chromophores such as water, opsins, hemoglobin, myoglobin,…

Wavelength

Lights with shorter specific wavelengths usually emit higher energy and vice-versa [81]. Each color of light that belongs to the visible light spectrum possesses a unique wavelength and based on the wavelength, lights are broadly categorized as lower (violet, indigo, and blue), middle (green, yellow, and orange), and higher wavelength lights (red). Generally, short and middle-wavelength lights activate TRP ion channels, opsins, flavins, and porphyrins while longer-wavelength lights activate CCO …

Oxidative stress

Oxidative stress is marked by an imbalance between the production of reactive oxygen species (ROS) and anti-oxidants [89]. Oxidative stress at appropriate levels is required for normal body functioning [89]. However, when the stress rises beyond a threshold it becomes detrimental and is one of the key stressors that leads to the development of various hallmarks of NDDs [90]. The CNS is particularly susceptible to ROS attacks mainly due to the presence of the BBB which limits the circulation of…

PBM increases blood flow and oxygenation

PBM with red and NIR lights significantly increases cerebral blood flow and subsequently oxygenation by increasing the release of nitric oxide which is a well-known vasodilator through photodissociation [192]. The released NO induces the formation of cyclic GMP (cGMP) which activates protein kinase G. Protein kinase G increases Ca^{2+} re-uptake and opening of calcium-activated potassium channels [193]. This activation prevents the myosin light-chain kinase from phosphorylating the myosin…

Nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB)

pathway

Increased oxidative stress usually witnessed in the case of neurodegenerative conditions actually activates IκB (an inhibitor of NFκB in its inactivated state), which is a pro-inflammatory transcription factor [207]. Once IκB is activated through phosphorylation and dissociated from NFκB then it gets targeted for proteasome-mediated degradation [208]. The freed NFκB then translocates to the nucleus and binds to DNA ultimately initiating the transcription of pro-inflammatory factors [208]. PBM…

Adenosine triphosphate (ATP)

Signaling mediated by ATP is referred to as purinergic signaling and in the nervous system, ATP is a well-known neurotransmitter and is often co-released with other neurotransmitters such as noradrenaline, and acetylcholine [250]. Purinergic signaling is important for neurogenesis and regulating neuronal apoptosis [251]. Aberrant purinergic signaling due to reduced ATP has been observed in the pathogenesis of many neurodegenerative diseases [252]. As discussed in previous sections, one of the…

PBM as a recuperation therapy

While many studies have focused on the direct effects of PBM in bringing down several features associated with PBM, there are many effects of PBM that would greatly aid in recovery post-treatment.…

Conclusion

In this review, various molecular mechanisms through which PBM confers beneficial effects against NDDs are discussed. The evidence presented in this review strongly supports the use of PBM as a promising therapeutic approach for NDDs. Literature with early findings suggests that photobiomodulation targets the key biological processes such as metabolism, inflammation, oxidative stress, and neurogenesis; hence PBM has significant clinical potential in the treatment of NDDs (Fig. 5). These…

List of chemical compounds

1. Glucocorticoids

1. Glucocorticoids…
2. Rapamycin…
3. Rolipram…
4. Memantine…
5. Vitamin E…
6. Formaldehyde…

…

CRediT authorship contribution statement

Pooja Ramakrishnan: Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Methodology, Conceptualization. **Aradhana Joshi:** Writing – review & editing, Writing – original draft, Investigation. **Mohamed Fazil:** Writing – original draft. **Pankaj Yadav:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Investigation, Funding acquisition, Conceptualization.…

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.…

Acknowledgments

The authors thank SASTRA Deemed-to-be University for the infrastructural facilities. All images were created using BioRender application.…

Funding

P.Y.: Science and Engineering Research Board (SERB), Department of Science and Technology (DST), Government of India, CRG/2019/003184. P.R.: Centre for Scientific and Industrial Research (CSIR) – Junior Research fellowship, 09/1095(15083)/2022-EMR-I.…

Recommended articles

References (278)

H.M. Gao *et al.*
Why neurodegenerative diseases are progressive: uncontrolled inflammation drives disease progression
Trends Immunol. (2008)

W.A. Rogers *et al.*
Envisioning the future for older adults: autonomy, health, well-being, and social connectedness with technology support
Futures (2017)

M.R. Hamblin
Shining light on the head: photobiomodulation for brain disorders
BBA Clin. (2016)

X. Yue *et al.*
New insight into Alzheimer's disease: light reverses Aβ-obstructed interstitial fluid flow and ameliorates memory decline in APP/PS1 mice
Alzheimer's Dement.: Transl. Res. Clin. (2019)

V. Ganeshan *et al.*
Pre-conditioning with remote photobiomodulation modulates the brain transcriptome and protects against MPTP insult in mice
Neuroscience (2019)

T. Karu
Primary and secondary mechanisms of action of visible to near-IR radiation on cells
J. Photochem. Photobiol. B Biol. (1999)

M.G. Mason *et al.*

Re-evaluation of the near infrared spectra of mitochondrial cytochrome c oxidase: implications for non invasive in vivo monitoring of tissues
Biochim. Biophys. Acta Bioenerg. (2014)

P.L.V. Lima *et al.*
Photobiomodulation enhancement of cell proliferation at 660 nm does not require cytochrome c oxidase
J. Photochem. Photobiol. B Biol. (2019)

M. Koyanagi *et al.*
Diversity of animal opsin-based pigments and their optogenetic potential
Biochimica et Biophysica Acta (BBA) - Bioenergetics (2014)

C. Regazzetti *et al.*
Melanocytes sense blue light and regulate pigmentation through Opsin-3
J. Invest. Dermatol. (2018)

View more references

Cited by (1)

Evaluation of the Impact of Near-Infrared Multiwavelength Locked System Laser Therapy on Skin Microbiome in Atopic Dogs ↗
2024, Animals

1 P.R.: Centre for Scientific and Industrial Research (CSIR) – Junior Research Fellowship, 09/1095(15083)/2022-EMR-I.

2 P.Y.: Science and Engineering Research Board, DST, Government of India, CRG/2019/003184.