Transcranial photobiomodulation for the brain: a wide range of clinical applications

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Photobiomodulation therapy (PBMT) is a rapidly growing approach to the healing, stimulation, protection, and regeneration of many human organs and tissue types. PBMT started in the 1960s as low-level laser therapy for wound healing, but since then the introduction of light-emitting diodes (LEDs) has dramatically increased the number of applications and reports of positive results. PBMT generally uses red (620–700 nm) and/or near-infrared (780–1270 nm) wavelengths of light at an intensity that causes no tissue heating, and its activity is based on well-established biological and cellular mechanisms (de Freitas and Hamblin, 2016). While laser therapists continue to use various types of laser in their office practice, LEDs are ideally suited for home use devices because they are completely safe and without any known significant adverse effects. Among the various body parts on which PBMT has been shown to exert

beneficial effects, the brain stands out as perhaps the most promising overall. PBMT has been shown to reduce neuroinflammation, while increasing mitochondrial function, oxygen consumption, and blood flow within the brain (Hamblin, 2016). Moreover, PBMT can stimulate the processes of synaptogenesis, neurogenesis, and neuroplasticity thus helping the brain to heal itself. PBMT has neuroprotective activity and can prevent brain damage in the acute phase after traumatic brain injury or stroke, because it inhibits apoptosis and upregulates the expression of anti-apoptotic proteins, as well as improving brain metabolism and oxygenation. In the chronic phase, PBMT can improve memory, cognitive function, mood, and sleep quality. In degenerative brain disorders (dementia, Alzheimer's disease, and Parkinson's disease), PBMT can improve motor, cognitive and social functioning (at least for some time). In a range of psychiatric disorders (depression, anxiety, autism spectrum disorder, and opioid addiction), PBMT can lead to significant improvements (Salehpour et al., 2018). This perspective will outline the mechanisms of action of PBMT on cells and tissues, and summarize the wide range of current applications to the brain, while proposing some new directions in psychiatry.

It was discovered some time ago that the principal chromophores (light-absorbing molecules) are located within the mitochondria. Cytochromes are involved in several

units of the respiratory chain (including cytochrome c oxidase), and they can absorb red/near-infrared light thus increasing electron transport and the mitochondrial membrane potential to increase adenosine 5′-triphosphate production. The raised mitochondrial membrane potential leads to a brief burst of reactive oxygen species in normal cells, but in dysfunctional mitochondria, the normalization of the mitochondrial membrane potential reduces the generation of reactive oxygen species and mitigates oxidative stress. There are also increases in nitric oxide and intracellular calcium, along with the activation of numerous transcription factors (de Freitas and Hamblin, 2016). Other chromophores have been suggested, including light and heat-sensitive transient potential ion channels, water surrounding adenosine 5′-triphosphate synthase, and direct excitation of oxygen by 1064 and 1270 nm lasers, but all of these mechanisms have also been proposed to affect the mitochondria. The activation of mitochondrial metabolism by PBM can be characterized as a switch towards oxidative phosphorylation and away from glycolysis. This switch has two important consequences. Firstly stem cells living in their hypoxic niche mainly rely on glycolysis for their energy requirements. However, when their mitochondria are activated by PBM they must leave their niche to go in search of sufficient oxygen to support oxidative phosphorylation. Once outside the niche, the stem cells become progenitor cells and can be influenced by any cues that might be

released from areas of tissue damage in order to differentiate into somatic cells where they can then repair the brain. The second consequence involves macrophages and microglia. These cells can be polarized into an M1 pro-inflammatory phenotype, which also mainly relies on glycolysis for energy production. However the counterpart M2 phenotype is anti-inflammatory, and the cells rely more on oxidative phosphorylation for their energy production. This M1–M2 switch accounts for the pronounced anti-inflammatory effects of PBM (Hamblin, 2017). illustrates the wide range of cellular and tissue mechanisms that have been proposed to play a role in the benefits of transcranial photobiomodulation. All of them have been shown to operate in at least some circumstances, while for each type of brain disorder, one mechanism may be more important than the others.

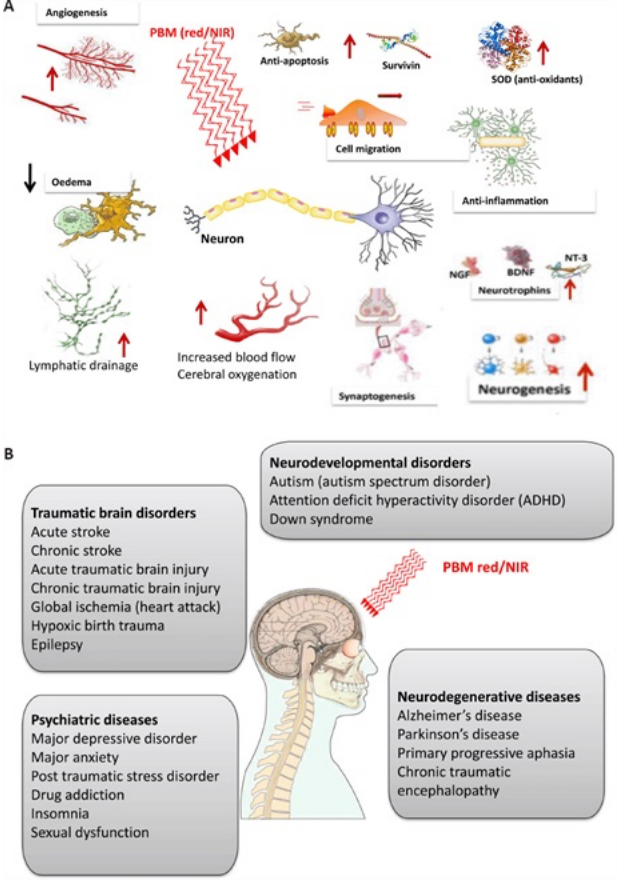

Figure 1:

Transcranial PBMT in the brain.(A) Illustration of cellular and tissue mechanisms that have been reported to occur with PBMT in the brain. (B) Brain disorders that could be treated with PBMT using red/NIR light delivered to the head, classified into traumatic, neurodegenerative, neurodevelopmental, and psychiatric disorders. Created with Microsoft PowerPoint. BDNF: Brain-derived neurotrophic factor; NGF: nerve growth factor; NIR: near-infrared; NT-3: neurotrophin 3; PBM: photobiomodulation; PBMT: photobiomodulation therapy; SOD: superoxide dismutase.

Because PBM mainly affects the mitochondria, it is not surprising that organs and tissues that are rich in mitochondria are some of the most popular targets for PBMT. These tissue targets include neurons, brain, spinal cord, retina, muscles, liver, and kidney. However, these mitochondria-rich tissues are generally located deep within the body, and it has been claimed that the light must be able to penetrate sufficiently deeply into tissue to have any

effect. This is an intriguing question because over the years it has become clear that in addition to the local effects of PBMT, there is also a pronounced systemic effect or action at a distance. In other words, light delivered to one part of the body can have beneficial effects on tissues and organs elsewhere. It is logical that these beneficial effects must be transported via the bloodstream, and the recent discovery of cell-free respiratory competent circulating mitochondria in blood might provide an explanation for this effect (Al Amir Dache et al., 2020). Because we are interested in the brain it is worth mentioning that the amount of light penetration through the human scalp and skull that reaches reach the cortical surface has been estimated at 1–2% depending on the wavelength and skull thickness (Salehpour et al., 2019). Nevertheless, it must be realized that when light is shone on the head it might be absorbed by the blood flowing within the scalp, or by the bone marrow located in the calvarial bone of the skull, so “transcranial PBMT” might work without actually being physically transcranial. There have been reports that PBMT can be effective in animals when the light is applied to remote areas of the body, or when the mice are simply allowed to run around under LED light delivered from the top of the cage.

There is a large body of work showing that PBMT is highly effective in treating models of various disorders of the brain and spinal cord created in laboratory animals, as well as

some genetically engineered mouse models such as Alzheimer's (AD) or Parkinson's disease (PD) (Hamblin, 2016). Due to space limitations, these reports cannot be discussed in any great detail. However, it is worth mentioning that animal models of a sudden brain insult, e.g., traumatic brain injury, stroke, and neonatal hypoxia-ischemia, can often be treated with a single exposure of the head to the light at a few hours after the insult. Degenerative diseases such as AD or PD usually require a repeated course of exposures at 1–2 day intervals for several weeks to show significant improvement in cognitive and motor performance. shows a broad overview of the wide range of brain conditions that have been treated with PBMT, classified into traumatic, neurodegenerative, neurodevelopmental, and psychiatric disorders.

There was a major effort to investigate the benefits of PBMT in patients who had suffered an acute ischemic stroke, when it was applied as a single treatment to the head within 24 hours of the stroke, as suggested by the good results from animal models. Despite encouraging results from the phase 1 and 2 trials, the large NEST-3 trial was discontinued early due to "futility" (Lapchak and Boitano, 2016). Several reasons have been put forward to explain the failure of NEST-3 in terms of the trial design being sub-optimal. Up to the present time, there have been only a few attempts to demonstrate the effectiveness of PBMT in the rehabilitation

of patients who were suffering from chronic stroke, despite several theoretical considerations suggesting it should be helpful.

Traumatic brain injury in humans has also been treated successfully with PBMT both in the acute phase as well as the chronic phase. Chronic traumatic brain injury patients required regular applications of tPBMT in order to maintain their initial improvements in memory and executive function. Chronic traumatic encephalopathy was also treated with PBMT administered by transcranial and intranasal routes in a case series of four ex-American football players. Cognitive improvements were confirmed by objective measurements of functional connectivity (resting-state functional magnetic resonance imaging) and metabolism (magnetic resonance spectroscopy) (Naeser et al., 2023).

There are several efforts underway to confirm the efficacy of tPBM in treating dementia and AD in humans after impressive success was shown in mouse models of AD. Recently, a randomized, double-blind, sham-controlled trial was reported using a combination of LED helmet and abdominal belt in 57 mild-moderate AD patients who received 40 treatment sessions lasting 25 minutes each over 8 weeks (Blivet et al., 2022). PBM-treated patients showed lower ADAS-Cog subscores, higher forward verbal spans, and lower TMT-B execution times.

Parkinson's disease has been treated with PBMT in Australia (Hamilton et al., 2018). The light has often been applied to the head as well as to other parts of the body such as the abdomen or the nose at the same time. PD symptoms including tremor, akinesia, gait, difficulty in swallowing and speech, impaired facial animation and fine motor skills, sense of smell, and social confidence, showed ~75% overall improvement after 30 minutes of PBMT daily for 10 days.

Autism spectrum disorder in adults as well as children appears to respond well to PBMT (Hamblin, 2022). One 8-week open-label study assessed the tolerability, safety, and efficacy of transcranial LED therapy in adult patients with autism spectrum disorder. An 830 nm LED array was applied to the forehead twice a week for 8 weeks. The patients that completed the study showed significant improvements in several scales related to autism spectrum disorder severity.

Psychiatric disorders such as major depression, generalized anxiety disorder, drug addiction, and insomnia have all been beneficially treated with PBMT administered to the head (Montazeri et al., 2022). Treatment-resistant depression would probably be the best indication at present. It is important to distinguish between PBMT and bright light therapy, which are both used for treating depression, but have very different mechanisms of action. Bright light therapy works via specific photoreceptors in the eyes, and

signaling in the brain related to circadian rhythms.

Overall, many of the clinical trials of tPBMT for brain disorders published so far have been pilot trials, and were underpowered to convince mainstream medicine to adopt this new technology. Additional larger trials will be required before tPBMT can become widely accepted in medicine and society at large.

The pronounced effects of PBMT in improving neuroplasticity and functional connectivity suggest that it may prove helpful in additional future applications. These could include post-traumatic stress disorder, attention deficit hyperactivity disorder, eating disorders (anorexia, bulimia), addictions (drugs, alcohol, gambling), chronic insomnia, and even schizophrenia. Some pilot trials for these indications would appear to be warranted in the near future.

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