

Introduction

Photobiomodulation of the Brain: Shining Light on Alzheimer's and Other Neuropathological Diseases

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Photobiomodulation (PBM) therapy refers to the non-thermal use of visible to near-infrared light (400 to 1100 nm) to stimulate many biological processes [1]. Nowadays, the applications of PBM therapy are extremely diverse in modern medicine, so that this light-driven modality has gained considerable credibility among the available therapeutic strategies. PBM therapy has been shown to be an effective strategy to promote microcirculation, cellular proliferation and regeneration, and to ameliorate pain, edema, oxidative stress, and inflammation in many traumatic, acute, and chronic diseases. Given this, there are numerous well-known medical applications where PBM therapy has a significant role to play, such as wound healing, muscle and tendon repair, autoimmune diseases, arthropathies, and esthetic applications [2]. The underlying molecular and cellular mechanisms of PBM therapy, rely on the absorption of photons by cytochrome c oxidase (CCO, the terminal enzyme in the mitochondrial

inner membrane respiratory chain) causing a redox change in the enzyme, leading to increased ATP synthesis and associated effects on cAMP and Ca²⁺, release of nitric oxide, and a burst in reactive oxygen species (ROS). These primary mediators, in turn promote a cascade of secondary events such as ROS-mediated activation of key transcription factors like AP-1 or NF-κB, and subsequent effects on transcription of genes involved in cellular processes such as proliferation and survival, as well as cell migration [3].

Brain PBM therapy is a promising modality by which red to near-infrared light emitted by lasers or light emitting diodes (LEDs) is delivered to the scalp to stimulate neural cells and brain function [4]. It is well known that photons in this wavelength range are able to penetrate the scalp/skull and partially reach the brain tissue [5]. Brain PBM therapy is safe, simple, pain-free, inexpensive, easy to administer, and well-tolerated by the patients in almost all clinical studies [6]. There is plenty of evidence suggesting the efficacy of PBM therapy in three major types of brain conditions; traumatic events (stroke, global ischemia, and traumatic brain injury), degenerative diseases (dementia, Alzheimer's and Parkinson's diseases), and neuropsychiatric disorders (major depression,

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bipolar disorder, anxiety, and post-traumatic stress disorder). Furthermore, in recent years, PBM has been gaining increasing interest as a brain-boosting strategy in healthy young and old individuals [7]. Brain PBM therapy has been shown to increase cerebral blood flow and also augment cerebral metabolic capacity. Moreover, there is growing preclinical evidence to support the hypothesis that brain PBM therapy could ameliorate neuronal oxidative stress, neuroinflammation, and apoptosis, and could also stimulate neurogenesis and synaptogenesis. In addition to the aforementioned beneficial effects at the neuronal level, there is also evidence of changes occurring at the neurobehavioral level such as cognitive improvement (in various domains, e.g., learning and memory, executive function, concentration, and attention), antidepressant-like effects, and improved sleep quality [8].

The aim of this Mini-Forum is to present the current state of the art in the application of photobiomodulation therapy for dementia, Alzheimer's disease, and other brain conditions. The first paper from the Mitrofanis group addresses the interesting question of whether direct PBM to the brain (either by a transcranial approach or an intracranial approach) is better than a systemic approach where the light delivered to the abdomen or leg to treat Parkinson's disease in animal models [9]. The next contribution from the Zhang group used transcranial PBM to treat the TgF344 rat model of Alzheimer's disease [10]. They found that spatial memory, anxiety, and depression were improved, while neuronal damage, inflammation, and oxidative stress were reduced. The next paper from the guest editors (Salehpour and Hamblin) is a systematic review of PBM for Alzheimer's disease and dementia both in preclinical models, as well as in dementia patients [11]. The fourth contribution is a systematic review from Caldieraro et al. on the use of PBM to treat patients with major depressive disorder, also looking at the relevance to Alzheimer's disease [12].

Chan et al. from Hong Kong reported a clinical trial using a single transcranial PBM session to improve memory in older adults with mild cognitive impairment [13]. Functional near-infrared spectroscopy showed that the hemodynamic responses during the memory tasks were lower after PBM. Another paper from Cassano's group used transcranial PBM to modify electroencephalogram activity and cerebral blood flow [14]. c-tPBM significantly boosted gamma and beta EEG spectral power in eyes-open recording and gamma power in eyes-closed

recording. The next paper from the Laakso group in Australia reports a randomized double-blind placebo-controlled pilot study on 22 patients with Parkinson's disease treated with a combination of transcranial PBM and intra-oral PBM [15]. The eighth paper from Korea describes an uncontrolled pilot trial of PBM in 14 patients with mild cognitive impairment [16]. PBM was applied to the neck overlying the arteries supplying the brain, and improved regional cerebral blood flow, as well as cognitive function, memory, and frontal/executive function. The final paper from a group in China describes a different type of light therapy, which is somewhat different from PBM [17]. This uses blue-green light from LED glasses delivered into the eyes to affect intrinsically photosensitive retinal ganglion cells, in an ongoing trial with 150 patients with mild cognitive impairment to improve cognitive performance, sleep, and mood.

We expect PBM to continue to be investigated to treat diverse brain disorders, considering the evidence of efficacy, almost complete lack of adverse effects, and the availability of relatively inexpensive LED devices that can be used at home.

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