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A Brief Review of Low-Level Light Therapy in Depression Disorder

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Abstract

Introduction: Low-level laser therapy (LLLT), also called Photobiomodulation, has gained widespread acceptance as a mainstream modality, particularly in the form of photobiostimulation (PBM). Here in our review, we aim to present the application of LLLT to help with depression, explore potential action mechanisms and pathways, discuss existing limitations, and address the challenges associated with its clinical implementation.

Methods: In biological systems, the visible light with a wavelength range of 400–700 nm activates photoreceptors involved in vision and circadian rhythm regulation. The near-infrared (NIR) light with a wavelength range of 800-1100 nm exhibits superior tissue penetration capabilities compared to the visible light, which enables the non-invasive application of LLLT to various tissues.

Results: By enhancing adenosine triphosphate (ATP) production using the respiratory chain, LLLT is able to enhance blood flow, reduce inflammation, support repair and healing, and enhance stem cell growth and proliferation. Preclinical studies using animal models have shown promising neuroprotective effects of the LLLT method on central nervous system (CNS) diseases, suggesting potential improvements in brain function for patients suffering from Alzheimer's disease. In addition, it helps Parkinson's patients with their movement problems and ameliorates mental disorders in individuals with depression.

Conclusion: patients' quality of life can be significantly enhanced. A comprehensive understanding of the protective effects and underlying mechanisms of LLLT will facilitate its therapeutic application in the future.

Keywords: LLLT; Depression; Photoreceptor cell; Near-Infrared.

Introduction

The utilization of sunlight for medicinal purposes has a long and interesting past, back to very old cultures and civilizations such as China, Egypt, and Greece, where it was known as heliotherapy.[1,2] Shortly after the groundbreaking discoveries of the first laser systems, namely the ruby laser (1960) and the helium-neon laser (He-Ne) (1961), these novel devices found their way into the realm of medicine. The pioneering research of physicist Dr. Maiman resulted in the invention of the first practical laser in 1960. Subsequently, the field of photobiostimulation (PBM) emerged as an area of study to explore the medical and therapeutic applications of lasers. Unlike the lasers in high-power class, which are able to lead to tissue photothermal damage, the focus shifted towards low-power lasers with the potential for healing, tissue preservation, pain mitigation, inflammation reduction, and regenerative medicine across diverse medical disciplines. In the past few years, the utilization of low-level laser therapy (LLLT) as a non-pharmacological therapy and intervention approach has gained significant attention due to its potential beneficial effects on the brain.[3-5] However, the emergence of LEDs, which are light-emitting diodes and alternative light sources for LLLT, caused some confusion in the field. While LEDs emit light similar to the available laser wavelengths, they lack the coherence characteristic of laser light and exhibit broader output peaks, making them less monochromatic. Consequently, the LLLT community is currently discussing the relative advantages of laser diodes versus LEDs. LEDs as low-power light sources on the milliwatt scale hold the advantage of being considerably more cost-effective than lasers.[6] The primary mechanism underlying LLLT involves the absorption of red wavelength light (600–750 nm) and near-infrared (NIR) one (800–1100 nm) by cells through chromophores present in tissues, including Flavin. This process leads to the increased activity of cytochrome C oxidase and subsequent enhancement of ATP synthesis.[2,7-11] Additionally, the absorption of low-energy light into ion channels leads to the release of calcium ions and thereby the activation of the transcription factors and the expression of the

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genes.[12,13]

The brain is an organ in the body that consumes the most energy.[14] Normal brain function depends on optimal metabolism and energy supply.[15] However, in many neurological diseases, energy metabolism and mitochondrial function are disintegrated, causing a vicious cycle of dysfunction. Depression, Alzheimer's disease, and Parkinson's disease are among the brain diseases characterized by a decrease in energy metabolism.[16-20] A fact is that mitochondria provide the necessary energy for cells to perform their expressive functions. Studies have shown that ATP can mediate antidepressant-like effects through cortical P2X2 receptors. With the progress of nervous system diseases, there is an essential need for therapeutic strategies to strengthen and restore brain energy.[16,21,22]

Depression is a serious emotional disorder with a considerable prevalence and recurrence rate that affects the quality of life and, in some cases, causes suicide. Apathy, unpleasant negative emotions, and sleep or eating disorders are some of the main symptoms of depression,[23] which can be caused by various factors such as biological, psychological, and social ones. The biology and mechanisms of depression are still unclear, and designing specific treatment plans has its own variety of challenges. Patients with more serious symptoms require longer treatment times and have a higher recurring rate. Consequently, there is a critical need for novel adaptable therapeutic approaches with minimal side effects.[24-27]

Low-power light therapy is a non-invasive photosynthetic approach that can be applied in the fields of neuroscience, psychiatry, and ophthalmology, and in recent years, the effects of LLLT on illnesses of the central nervous system (CNS) have been demonstrated in animal studies. LLLT can not only moderate oxidative stress but also raise ATP synthesis for improving mitochondrial function. It also acts on specific neural circuits to provide treatment as a depressant. However, its neuroprotective mechanism remains to be further elucidated.[28-30] In this review, we aim to cover the probable mechanisms by which LLLT produces neuroprotectors and their impact on depression. In addition, we will discuss new approaches regarding the CNS and the benefits of LLLT for treatment, daily care, and disease prevention.

Low-Level Light-Tissue Interaction

Concurring with the primary law of photobiology, photons of the light must be absorbed by the electronic bands of the cells' chromophores for low-power light to have an impact on a living biological system. Investigating these pigments using optical spectroscopy is one way to determine their identity. Similar to the absorption spectra of photoreceptor molecules, the absorption spectra of the chromophores represent the distinct nature of tissue or living cells at various wavelengths. The fact that the spectrum describes the quantum structure of target molecules supports the idea of the existence of cellular receptors and signaling in light-stimulated pathways. Some studies confirm that the red to NIR wavelengths can be absorbed by cytochrome C oxidase (CCO).[31] Primary cellular effects are generally related to the interaction of photons with intracellular components like cytochromes (Figure 1). Visible-NIR light radiation can be absorbed by cytochromes, which are located in mitochondria.[32] It

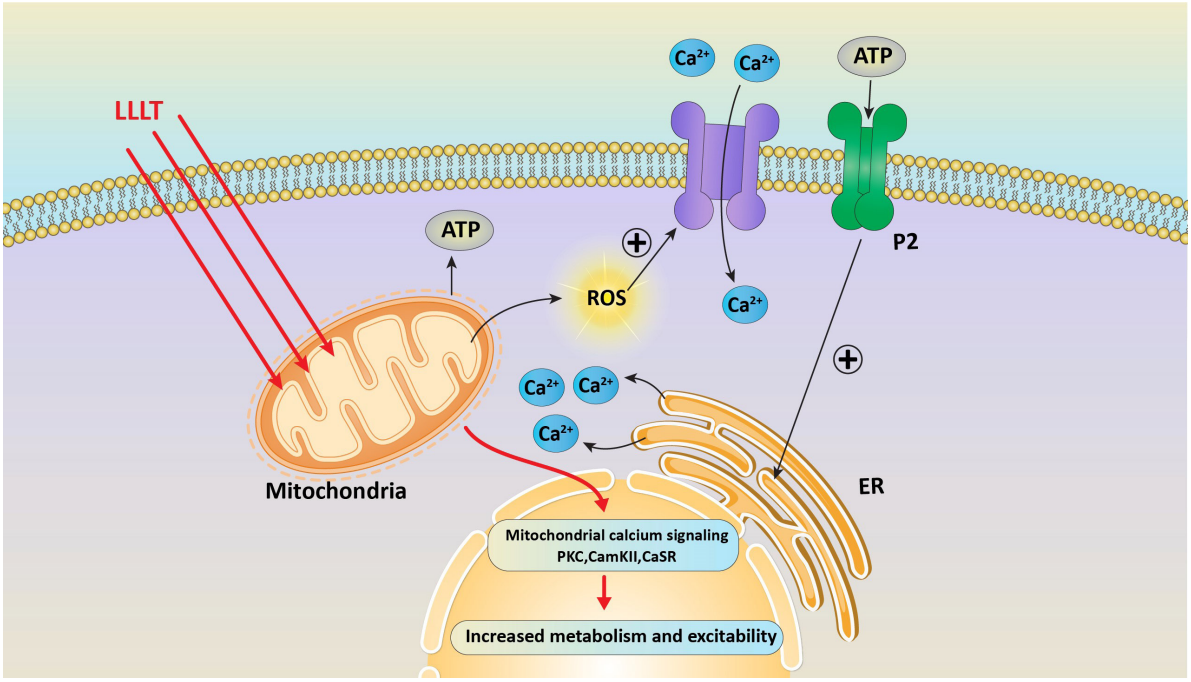

Figure 1. The Cellular Pathway in LLL-Tissue/Cell Interaction

is also assumed that light can act as a catalyst and affect molecules, organelles, and cells without absorption.[33]

As it is presented in Figure 1, low-level light is absorbed by the mitochondrial chroromophore, most probably CCO. The interaction of light and CCO increases mitochondrial membrane potential, leading to a rise in ATP synthesis and causing some amounts of reactive oxygen species (ROS), Ca^{2+}, and nitric oxide (NO). Additionally, there is communication between the mitochondria and the nucleus, which is caused by changes in the mitochondria. These alterations modify ATP synthesis, intracellular redox potential, pH, and concentration of the cyclic adenosine monophosphate (cAMP). Mitochondrial calcium signaling changes ion flux at the cell membrane and membrane permeability, leading to an increase in metabolism and excitability.[34]

The interaction of LLLT with tissues is influenced by such parameters as tissue absorption coefficient, laser wavelength, energy density (including pulse length and frequency), polarization, interaction time, and wave properties due to the intrinsic wave of light.[35] There are some facts indicating that pulsed light (laser or LED) is also affective for treatment differently from continuous wave (CW) mode. Previous research has defined that pulsed light appears to be more effective than others in triggering desired biological pathways and processes.[36,37] Hence, it is vital to select optimized irradiation parameters in a treatment plan to obtain a more substantial therapeutic outcome.

The Neuroscience of Depression

Major depressive disorder is a common impairing mental illness that has a significant effect on the quality of life and negative effects on mood, behavior, and mental perception.[38] Globally, approximately 5% of the world's population suffers from depression.[39] In recent decades, various mechanisms in the pathophysiology of depression have been investigated, including changes in noradrenergic, dopaminergic, and glutamatergic systems, escalated inflammation, abnormalities of the hypothalamic-pituitary-adrenal axis, vascular changes, decreased neurogenesis, and neuroplasticity.[40]

The ketamine-induced glutamate burst stimulates signaling pathways that promote synaptic growth. This includes the activation of the complex that is the mammalian target of complex 1, which regulates the translation of synaptic proteins required for the formation of new synapses. It is considered to have caused synaptic plasticity in long-term memory.[41]

The behavioral indications of sadness and depression are wide and broad. They cover affective, motivational, cognitive, and physiological domains and include apathy, abnormal reward-related perception, and memory changes.[42-45] Currently, major depressive disorder is considered to be a multifactorial disease with various causes and triggers, including genetic susceptibility, stress, and other pathological processes such as inflammation. For example, in some cases, genetic factors can cause depression. It should be emphasized that depression is a heterogeneous disorder, including many subtypes (melancholic, atypical, psychotic, etc.) with different characteristics in terms of symptoms, neurobiology, reproductive function physiology, and endocrine.[45] A multitude of symptoms associated with depression are most likely the result of anomalies in numerous elements of normal brain processes, which can range from the molecular to the neural circuit level [46]. Lack of activity, stress, and maternal deprivation can reduce both brain-derived neurotrophic factors (BDNFs) and neural activity in the brain (Figure 2). This leads to cognitive decline or atrophy and neuronal cell death, in which the final result might be depression or Alzheimer's.[47]

Major depressive symptoms appear to be associated with the disruption of a widespread neural network that encompasses cortical and limbic areas rather than a functional breakdown of a particular brain region.[48]

Low-level Light Therapy in Depression

Currently, antidepressant medications are based on the monoaminergic neurotransmission theory, which results in a rise in the 5-hydroxytryptamine (5-HT) or norepinephrine brain levels as antidepressants with side effects.[49] Patients suffering from depression exhibit mitochondrial dysfunction and energy metabolism abnormalities in many areas of the brain,[50,51] as well as trouble focusing and weariness, which may be characterized by a lack of energy.[52] As a result, CCO

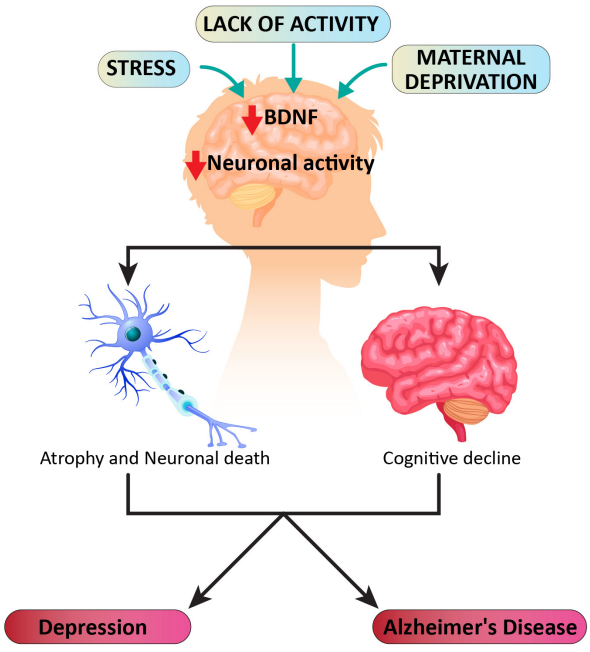

Figure 2. Model of Depression Progression

might be an implicit target for LLLT to mitigate depression through the skull, in which NIR photon energy is transferred via the scalp by LLLT to the cerebral cortex (Figure 3). Some preclinical investigations have shown that following LLLT, the expression and activity of ATP synthase and mitochondrial complex greatly increased in the prefrontal cortex (PFC) and may improve the depression-like tendency in mice.[53] To achieve antidepressant effects, LLLT can increase neurotransmitter levels, specifically 5-HT in the PFC, as well as NO levels.[54] BDNF has antidepressant and neurogenesis properties that can help with the illness.[55,56] Some researchers have discovered that LLLT increases BDNF expression in hippocampus neurons via the oxidative stress mechanism.[57] Furthermore, depression is thought to be linked to inflammation and oxidative stress.[57] Because LLLT has been proven to have anti-inflammatory properties as well as the potential to reduce the excessive formation of ROS in the oxidative damage process, it may be useful for treating depression.[58-60]

For depression receptors, LLLT may improve glutamate receptor activity via glutamate transporter-1 (GLT-1)-mediated glutamate uptake in the cerebral cortex, and hippocampus by boosting and stimulating the expression of α- amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors. Thus, it can reduce glutamate excitotoxicity and improve depression side effects and complications.[61]

We can take advantage of the unique low-energy light to execute the non-invasive combination approach or to boost favorable signaling pathways by engaging molecular signals. Deeper penetration is vital for the application of LLLT to reach deep brain tissues and activate preventive or regenerative processes, as well as preventing muscular atrophy in individuals who have lost their capacity to move normally. Furthermore, boosting the production capacity of mitochondria in healthy cells might cause sick cells' living spaces to be compressed. Non-specific photoreceptor components have a wide range of applications in photodynamic and optogenetic treatment.[62,63] Specific wavelengths are able to be tuned using up-convergent nanoparticle materials. NIR light that penetrates deeper into tissue is thought to either activate the ventral tegmental area to deliver dopamine or suppress and control brain cell activity and the habenular nucleus, on which there are numerous studies demonstrating the hyperactivity of lateral habenula neurons in patients with depression.[64] CCO, light-sensitive chromophores in critical pathways, appears to be the target of LLLT in neuronal tissue. It should be noted that, for brain tissue, which is a complex biological system composed of various chromophores in a deeper targeted area, it is critical to apply light photons in a longer wavelength regimen to deliver the desired light, and penetration facilitates clinical applications. LLLT is now integrated into traditional medicine, along with ongoing research to verify its effectiveness. There are downstream signal pathways following the LLLT in which neuroprotective mechanisms are initiated for the improvement of neural disorders. Until now, there have

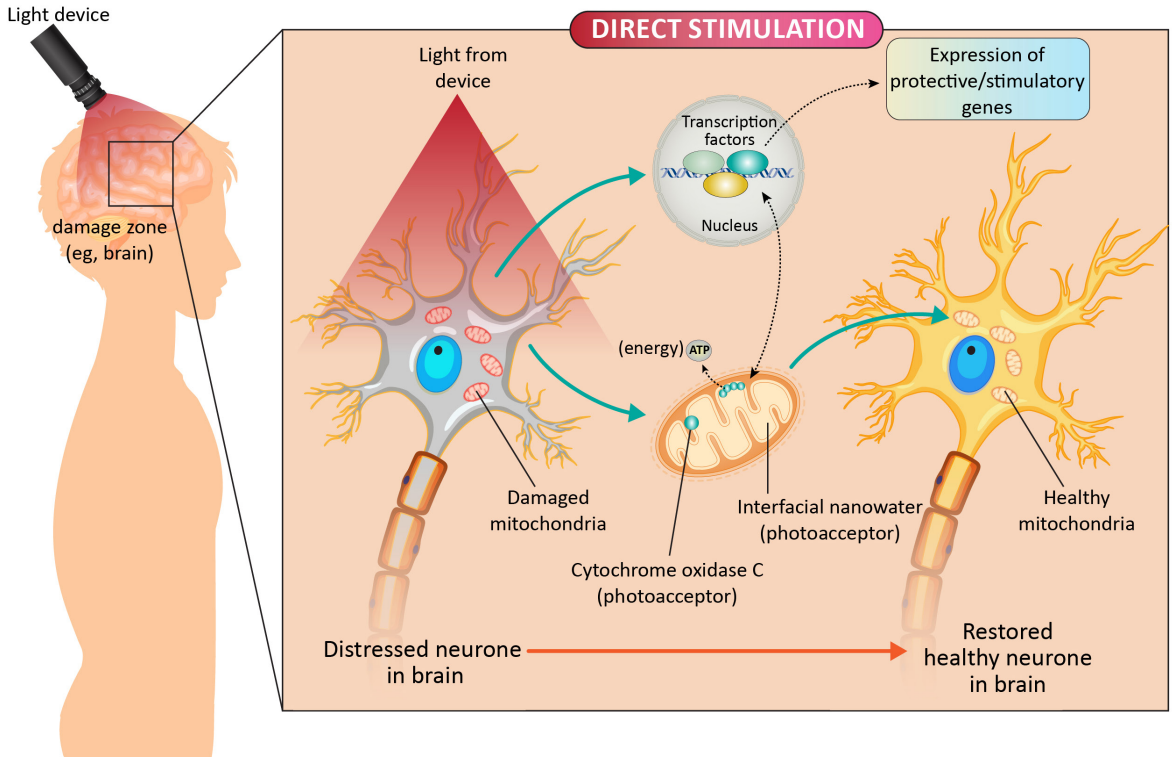

Figure 3. Schematic Diagram Showing the Direct Stimulation Mechanism of LLLT

been NIR physical therapy tools for the rehabilitation of musculoskeletal diseases, while the light energy density should be optimized based on the patient's conditions for achieving the goals based on precision medicine. In other words, the key point is that the effects of LLLT appear to be influenced by specific light irradiation parameters. The main function and role of LLLT in the treatment of CNS abnormalities have not yet been generally understood. More clinical facts and evidence are crucial for a deeper understanding of the improvements. The neuroprotective mechanisms and psychological benefits due to LLLT are interesting research areas from bench to bed.

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Competing Interests

The authors declare no conflict of interest

Ethical Approval

Not applicable.

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