The Effects of Low-Level Light Therapy in Patients with Neurodegenerative and Neurodevelopmental Disorders

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Abstract

Low-level light therapy (LLLT) has been used to treat wounds, pain, inflammation, and cancer for decades. LLLT applies light quanta to stimulate a biological response. Recently, researchers have shifted the focus of studies to the application of LLLT on brain disorders. During the past decade, LLLT has been widely used to affect neurological and psychological diseases such as depression-like behaviors, Alzheimer's disease (AD), Parkinson's disease, stroke, and traumatic brain injury. Because red or NIR light can effectively penetrate brain tissues, LLLT can play a beneficial role in increasing ATP biosynthesis and neurogenesis. Research has focused on LLLT for TBI, depression, and AD. Transcranial LLLT improved neuromuscular performance, increased brain-derived neurotrophic factor (BDNF), reduced brain lesion volume, enhanced learning and memory, and overall improved the neurological severity score in mouse models of TBI. Clinical studies show that LLLT improves cognition and decreases depression, anxiety, headache, and insomnia in patients with chronic TBI. Thus, LLLT could serve as a new practical approach for the management of TBI. There is no medical panacea for patients with neurodegenerative and neurodevelopmental disorders such as depression, autism, and Alzheimer's disease (AD), Parkinson's disease, stroke, and TBI. The need for novel treatments offers researchers the opportunity to explore new technology for these disorders. LLLT is a novel therapeutic approach based on photon irradiation to biological tissue, and it has been used to treat brain disorders. Although there are individual therapeutic options for neurodegenerative and neurodevelopmental disorders, there is little available nonpharmaceutical receptor-based afferentation therapy. In this review, the focus is on a growing body of evidence surrounding the therapeutic effects of LLLT for neurodegenerative and neurodevelopmental disorders. Therefore, in this paper, the objective is to provide an extensive review of the

literature examining the effects of Low-Level Light Therapy (LLLT) in patients with neurodegenerative and neurodevelopmental disorders. LLLT can enhance ATP biosynthesis, regulate mitochondrial homeostasis, and facilitate neurogenesis and neuroplasticity. However, understanding of the cellular and molecular mechanisms underlying the therapeutic benefits of LLLT on these disorders are still at early stages; therefore, clinical trials on neurodegenerative and neurodevelopmental disorders treated with LLLT are critical for future epidemiological studies.

Keywords: *Low-Level Light Therapy, photobiomodulation, depression, autism, and Alzheimer's disease (AD), Parkinson's disease, stroke, traumatic brain injury, mitochondria.*

Introduction

Low-Level Light Therapy (LLLT) comprises therapeutic approaches that apply the Photobiomodulation (PBM) principle to initiate biological alterations through the interactions of photons in light and molecules in tissues (Hamlin, 2019). The therapy serves various functions such as regenerating, preserving and stimulating tissues as well as cells. Research (cite) indicates that LLLT involves the irradiation of tissues and cells using low-powered light quanta to cause biological alterations in the dosed tissues. The first application of LLLT was documented in 1967 when it was used to ameliorate] tumors. LLLT applications have expanded over the years to treat both neurodegenerative and neurodevelopmental disorders. Neurodegenerative disorders are caused by progressive neuronal death, causing maladies such as Parkinson's Disease (PD) and Alzheimer's Disease (AD) (Johnstone, 2016). Neurodevelopmental disorders result from the disturbance of the Central Nervous System (CNS), causing brain dysfunction and such effects as impaired intracellular communication. This paper discusses the implications of LLLT in patients with neurodegenerative and neurodevelopmental disorders.

Parkinson's Disease and Alzheimer's Disease

LLLT is commonly known as photobiomodulation (PBM). Studies indicate that PBM causes various effects in patients with PD. Researchers have demonstrated PBM's neuroprotective abilities in patients with PD. Investigators argue that the neurodegenerative disorder results from "degeneration of dopaminergic neurons" in the brain, causing reduced control of movement. Studies conducted to demonstrate the effects of PBM on PD reveal that administration of PBM protected the dopaminergic cells in the brain from toxicity (1). Moreover, experiments conducted with "tau transgenic mice" reveal that LLLT reduces hyperphosphorylated tau. The reduced expression of the hormone decreased the degeneration of cells due to the reduction of tau-caused oxidative stress (1).

Additionally, clinical evaluations show that LLLT positively influences PD symptoms (2). These symptoms comprise bradykinesia and posture degradation. The use of LLLT in Parkinsonian patients exhibiting movement and posture deficits results in functional improvement. Of note is that research determinations importantly warn that the symptoms worsened with the administration of high-light doses. Hamilton et al. (2018) suggest that LLLT increases the levels of tyrosine hydroxylase (TH+). The levels of TH+ determine the functioning of dopaminergic cells; increased levels indicate improved functioning of the cells, exhibiting the neuroprotective abilities of LLLT (2).

Studies conducted in cortical and striatal cells of rats exposed to 1-methyl-4-phenylpyridium (MPP+) and rotenone (C23 H22 O6) revealed that LLLT reduced oxidative stress, increased adenosine triphosphate (ATP) content, and reduced the death of cells. Additionally, LLLT has shown the potential to improve the functioning of mitochondria in human neuroblastoma cells (3). Various studies have linked PD to mitochondrial dysfunction.

The increased functioning of mitochondria implies that the patient experiences reduced adverse effects of PD (3). Parkinsonian patients have difficulties controlling their movements. LLLT helps to improve the mobility of mitochondria along the axons. The improved action restores the control levels of the patients, thus enabling them to move about comfortably.

Further analyses indicate that LLLT saves dopaminergic cells from dying (4). Report findings suggest that the application of the therapy during, as well as after or before, an insult rescued the damaged neurons and conditioned the healthy neurons to further protect other cells from subsequent stressors. The rescue property is essential for Parkinsonian patients that have already suffered significant neuronal loss through degeneration. Monkeys exposed to LLLT experimentation had a higher number of striatal terminations and surviving cells compared to those in the control group. LLLT applications increase the survival of dopaminergic cells in the brain to prevent the over-expression of Parkinson's disorder symptoms (4).

Additionally, researchers have shown that LLLT corrects abnormal activities of neurons resulting from Parkinson's (5). Studies indicate that LLLT reduces the "overactivity" of firing neurons in the brain, primarily in the subthalamus, which is a neurophysiologic activity common in people with Parkinson's. However, the action is partial since the reduction does not achieve the required control levels and the partial restoration results from the repair of dopaminergic cells. The repair causes the cells to release dopamine, thereby improving the motor behavior in patients. Experiments conducted on mice reveal that LLLT treatments improved motor behavior by upgrading locomotion parameters such as velocity and mobility (5). The experimental group was observed to exhibit enhanced control-locomotion compared to the untreated mice. Other experiments relating to symptom severity showed that LLLT tends to reduce the expression of the symptoms in treated mice. Human subjects have demonstrated similar results.

Most of the studies examining the effects of LLLT in Alzheimer's patients have found beneficial outcomes in animal models. Experiments using transgenic mice have shown that LLLT treatment results in decreased amyloid levels in the brain (6). Moreover, LLLT reduced "A-Beta Plaque numbers." Advanced amyloid deposition results in extreme behavioral effects. The research with mice shows that LLLT reduces the behavioral effects and the inflammatory markers in the experimental group. LLLT reduces the cell damage markers in the brain and the pathological hallmarks associated with Alzheimer's disease (6). In AD-patients, LLLT aids the restoration of mitochondrial markers such as cytochrome c oxidase that facilitate the survival of neurons (6). These markers help to inhibit or suppress the effects of the AD condition.

There are limited clinical trials of LLLT on Alzheimer's patients. The few existing works indeed demonstrate the improvement of patients with the administration of LLLT (7). Russia was involved in conducting some of the most robust clinical trials. During these trials, the investigators used intranasal and a Vielight Neuro device to administer 25-minute per session treatments daily for one year. Monitoring reports specify that the cognitive abilities of the patients significantly improved with this care plan (7). Both the memory and cognition of the patients experienced significant improvements. Baseline scores of "significant cognitive impairment" recorded "no cognitive impairment" scores at the end of the treatment period. These therapeutic benefits indicate that LLLT slows the neurodegenerative process. The clinical trials document that patients failing to adhere to the guidelines of the treatment plan did not achieve much success. Therefore, this research supports that LLLT has positive effects on AD-patients, which may be associated with its pro-metabolic properties. These properties improve the cognitive abilities of AD patients (7).

Other researchers have reported that LLLT increases the overall number of brain cells in Alzheimer's patients and reduces the B-amyloid aggregates (8). The increase in the number of cells is associated with the improved functioning of mitochondria. Furthermore, there are clinical experiments that have reported improved learning and executive functioning after LLLT. Patients suffering from traumatic brain injuries have shown improved conditions when put under LLLT. Other researchers report that LLLT improves cerebral microcirculation that permanently reduces cognitive recovery and dementia. These effects show that LLLT suppresses the progression of most neurodegenerative disorders (8). However, there is no conclusive evidence concerning the effectiveness of PBM treatment on Alzheimer's patients. Most of the clinical trials are in the early stages, and precautions should be taken that all LLLT procedures be administered by trained professionals with extreme care to avoid possible adverse effects in mammals.

Chronic Traumatic Brain Injury

Investigators indicate that LLLT offers positive outcomes to patients struggling with neurodevelopmental conditions such as chronic traumatic brain injury (TBI). Patients with this neurodevelopmental disorder have neurological characteristics such as increased microglial activity, which in turn creates chronic inflammation. Moreover, chronic TBI causes abnormalities in the axons of the white matter, causing decreased brain interconnectivity (9). The reduced brain interconnectivity significantly correlates with reduced functioning of the Salient Network (SN), Central Executive Network (CEN), and the Default Mode Network (DMN) systems. These networks are responsible for vital brain interconnections that facilitate brain functions such as cognitive reasoning. Failure to initiate the interconnections results in cognitive

impairments and interferes with other functions such as language processing and communication (9).

Patients with difficulties deactivating the DMN system experience reduced cognitive performance because the system cannot switch rapidly between the networks (10). Additionally, reduced cognitive functioning can cause sleep disturbances. Chronic TBI patients have reduced ATP production, causing ATP to lie below the recommended homeostatic levels. Research again suggests that LLLT is an effective treatment to mitigate most of the symptoms associated with chronic TBI (10). Various treatment models indicate that LLLT boosts synaptogenesis to improve neural interconnectivity, thereby enhancing cognitive abilities.

Again, LLLT applications heighten the production of ATP and reduce inflammation. Some of the Chronic TBI patients treated with LLLT have shown improved verbal memory and language processing. These improvements result from the increased interconnectivity and switching between the networks affected by the disorder (10).

Neurogenesis and Synaptogenesis

Researchers identify that many neurodegenerative diseases are associated with poor neuronal connections and the death of cells in the brain. LLLT helps to prevent the progression of mood disorders and neurodegenerative diseases by promoting neurogenesis and synaptogenesis (11). LLLT stimulates the regeneration and rewiring of neurons, thereby preventing the harmful effects of these conditions. LLLT regulates Brain-Derived Neurotrophic Factor (BDNF) to aid neuronal connectivity. BDNF is a protein located in the central nervous system that maintains the existing neuron network and encourages the development of new synapses and neurons (11).

Most neurodegenerative diseases cause the death of neurons by interfering with the proteins making up the neurons. Proteins such as BDNF modulate the structure of dendrites improving synaptic transmissions. Studies show that LLLT uses the CREB protein pathway to slow the attenuation of BDNF, thereby affecting the morphogenesis of dendrites and enhancing the connectivity of neurons (11).

Research also indicates that BDNF mediates protein synapsin 1; this protein is crucial in strengthening synaptogenesis, as it helps to maintain the contact of synapses and facilitates the development of neurons (12). Studies associated with the protein identify that patients treated with LLLT show increased activity of the proteins. For instance, experiments indicate that patients with adequate BDNF that were exposed to LLLT experienced increased interconnectivity of the neural tissue fibers. The increased interconnectivity implies that the irradiations activated the neurons in the brain to regenerate and connect essential networks such as the SN and the DMN (12).

LLLT affects neurodegenerative disorders by manipulating stem cells. Neurogenesis is the primary objective for the management of neurodegenerative diseases because it serves to replace the damaged neurons and cells. By manipulating stem cells, BDNF helps to improve neurogenesis by optimizing the repairing of damaged tissues (13). In patients battling neurodegenerative diseases, LLLT has shown efficacy in promoting the migration, differentiation, and proliferation of cells. These aspects are essential in determining the success of stem cell therapies. Stem cell therapies help to reduce the symptoms of neurodegenerative and neurodevelopmental disorders by regenerating the damaged tissues (13). Once most organisms have matured, remaining stem cells tend to be dormant in the brain. These cells can only be

useful if they are activated to facilitate the regeneration process. LLLT treatments help to activate the stem cells, thereby promoting the regeneration of neurons.

Importantly, LLLT facilitates the production of neural progenitor cells in large quantities (14). These cells have similar functions to neural stem cells. They help activate the regeneration of new cells and positively influence the neurogenesis process. Such positive effects help patients experience reduced adverse effects due to their disorders (14).

Gamma Rhythms

Recent research indicates that LLLT treatments induce gamma rhythms in patients with neurodegenerative and neurodevelopmental disorders (15). These neural oscillations serve various purposes, such as strengthening neuroprotection, reducing neurodegeneration, and enhancing cognition. Additionally, these rhythms improve the functioning of synapses and reduce the damage of DNA in the neurons, which help to reduce amyloid plaques. Reducing amyloid plaques provides numerous benefits, such as improved cognitive functioning (15).

Anti-inflammatory Effects

Research again supports that chronic inflammation is a cornerstone of many infirmities, including neurodegenerative diseases. Inflammation hinders the effective connectivity of the neurons (16). Therefore, chronic inflammation causes impaired cognitive functions and impaired motor control functions. Most immune systems use various degrees of inflammation as defense mechanisms against viruses, bacteria, and other survivability threats. Acute inflammation, however, is necessary for human homeostasis (16). On the other hand, chronic inflammation results in complications such as mood disorders. Researchers have found that LLLT helps patients with neurodegenerative diseases to quell inflammation. The therapy works by inhibiting the cyclo-oxygenase 2 (COX-2) enzyme (16). Extant literature suggests that low power light

irradiations decrease the intracellular reactive oxygen species (ROS) to inhibit the COX-2 enzyme (17). The inhibition prevents inflammation when the body detects viruses, bacteria, and other threats. Since the discovery of LLLT's inhibition properties, the therapy has gained vast applications. In our current healthcare system, physicians use pharmaceutical approaches to inhibit the COX-2 enzyme (17). LLLT is applied in many cases to reduce detrimental inflammation safer and with less overall costs than drugs.

Furthermore, LLLT has abilities to modulate essential cytokines that regulate inflammation. The levels of these cytokines determine the signaling functions of the immune system (18). Various experiments have shown that LLLT controls the levels of anti-and pro-inflammatory cytokines. These cytokines are essential in controlling inflammations in the neural system. For example, the ability of LLLT to regulate the levels of pro-inflammatory cytokines and TNF (Tumor Necrosis Factor) helps to reduce neural inflammations (18).

Another positive effect of LLLT in patients with neurodegenerative diseases is that photo-biomodulation (PBM) activates the metabolism of mitochondria from aerobic glycolysis towards oxidative phosphorylation (19). This effect of PBM has the potential to change the phenotype of microglial cells from M1 to M2. The M1 phenotype cannot dispose of beta-amyloid plaque substances in AD patients. Therefore, the M1 phenotype facilitates the generation of inflammatory cytokines and ROS (19). The M2 phenotype has opposite effects compared to M1. The M2 phenotype exerts anti-oxidant and anti-inflammatory effects on cells. Therefore, the changing of phenotypes would enable the clearing of plaques and encourage the healing of tissues because of the anti-oxidant effects (20). Analyses indicate that the M1 phenotype is associated with shifting to aerobic glycolysis to enable energy production. Energy

production helps to promote the survival of cells and enhance the activation of microglia to manage most of the symptoms associated with neurodegenerative disorders (20).

Brain Monoamine Transmitters

Research points out that many neurodevelopmental conditions are associated with anxiety and depression disorders (21). Investigators suggest that depression symptoms are related to aberrations with monoamine neurotransmitters such as norepinephrine, serotonin, and dopamine. Analyses indicate that the etiology of depression and anxiety disorders depends on neural transmitters. For instance, serotonin is responsible for regulating brain activities such as emotions and memory. Dopamine regulates excitement and happiness. These neurotransmitters determine the depressive symptoms in patients battling neurodevelopmental disorders. Studies indicate that LLLT can improve the levels of these neurotransmitters in the brain to inhibit depressive-like symptoms (25). Experiments conducted with patients exhibiting depressive-like symptoms reveal that LLLT treatment reduced depressive symptoms by enhancing the levels of dopamine and serotonin in the brain (21). That is, the increased concentration of the monoamine transmitters helped to reduce the depressive effects.

Regulation of Downstream Signaling Pathways

Experiments indicate that LLLT induces Pheochromocytoma (PC12) cell apoptosis. The therapy achieves the above process by increasing the Bax mRNA levels. The action depends on the regulation of Bax using the pathway activated by protein kinase C. Further studies identify that LLLT enhances the T-cell factor and the translocation of proteins, such as B-catenin, which are essential in the treatment of AD symptoms (22). AB-induced apoptosis enhances pro-survival of the cells, thereby promoting downstream signaling. Different experiments identify that LLLT facilitates the working of SH-EP cells in the human neuroblastoma by preventing the aggregation

of the protein AB. The results indicate that LLLT could enhance therapeutic outcomes in patients with AD (22).

Inhibiting Effects of Toxins

People suffering from neurodevelopmental and neurodegenerative disorders may have been exposed to toxins (23). Exposure to toxins such as ethanol and methanol harmfully affect the neural network impairing functions such as cognition, language processing, and motor functioning. These toxins generate damaging effects by forming acids that inhibit essential enzymes such as COX (24). Analyses indicate that LLLT helps to eliminate the detrimental effects of the toxins to facilitate the functioning of such essential enzymes. The absorption of COX increases minimum miscibility pressure (MMP) in the neural networks and increases the production of ROS. LLLT increases MMP by addressing the associated effects such as oxidative stress and excitotoxicity. Increasing the MMP in patients helps to decrease the production of ROS in the cells, increasing their chances of survival (24). Moreover, LLLT inhibits the harmful effects caused by potassium cyanide, thereby preventing potential apoptosis (23). These intracellular events reduce the adverse consequences of neurodegenerative and neurodevelopmental disorders in humankind.

Conclusion

As a non- pharmaceutical therapeutic approach, accumulated evidence from various studies has shown that LLLT is a beneficial treatment for patients with neurodegenerative and neurodevelopmental disorders such as depression, autism, and Alzheimer's disease (AD), Parkinson's disease, stroke, and chronic traumatic brain injury. With the increasing enthusiasm for studies on LLLT, the cellular and molecular mechanisms of LLLT are still in the early stages of understanding (7). LLLT biological effects are likely related to factors such as the

mitochondrial oxidative respiratory chain, Akt/YAP/p73/GSK3 β/PKC signaling, neurogenesis, neuroplasticity, and monoamine neurotransmitters (23). However, the primary mechanism of LLLT is closely related to the function of the mitochondria in pathophysiological conditions. Mitochondria may be the essential organelle within cells governing the LLLT responses. Although the single and multiple applications of LLLT at the surface of the cerebral cortex appears to be safe within one year after treatment in animal models, LLLT, as a new therapeutic technology, needs more studies to prove its safety (22). Besides, there is a need to examine the effects of LLLT including most clinically useful and condition-specific wavelengths of light, dose intensity, irradiation mode, and the duration of LLLT care plans on physiological and pathological conditions (16). Further, other cellular and molecular mechanisms responsible for the biological effect of LLLT are additional topics requiring investigation (25). In conclusion, LLLT will shed new light on the treatment of neurodegenerative and neurodevelopmental disorders.

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