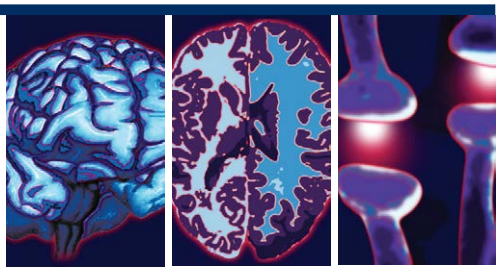
Review



Transcranial Low-Level Laser Therapy for Depression and Alzheimer's Disease

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Abstract

There is no effective therapy in patients with depression and Alzheimer's disease (AD). The need for novel treatments offers researchers the opportunity to explore new technology for these disorders. Transcranial low-level laser therapy (LLLT) is a novel therapeutic approach based on laser irradiation to biological tissue, and it has been used to treat brain disorders. Although there are certain therapeutic options for depression and AD, there is little treatment available as non-invasive physical therapy. In this mini-review, we focus on a growing body of evidence surrounding the therapeutic effects of LLLT for depression and AD. Transcranial LLLT can enhance ATP biosynthesis, regulate mitochondrial homeostasis, and facilitate neurogenesis and/or neuroplasticity. However, the cellular and molecular mechanisms underlying the treatment of LLLT on these disorders are still at early stages. Clinical trials on depression and AD by transcranial LLLT are critical for future studies.

Keywords

Low-level infrared laser, Depression, Alzheimer's disease, Mitochondrion

Introduction

Low-level laser therapy (LLLT) was discovered 50 years ago and has been used to treat wounds, pain, inflammation and cancer [1]. LLLT applies low-powered red or near-infrared (NIR) laser light (1-500 mW of power levels and 600-1100 nm of wavelengths) to stimulate a biological response [1]. These lasers generate a thermal effect without heating, sound, or vibration [1]. It belongs to class 3 of laser classification. Recently, researchers have shifted the focus of research to the application of LLLT on brain disorders [1-3]. During the past decade, LLLT has been widely used to study neurological and psychological diseases [3] such as depression-like behaviors [4-8], Alzheimer's disease (AD) [9-20], Parkinson's disease [21], stroke [22,23] and traumatic brain injury (TBI) [24-32]. Because red or NIR light can effectively penetrate into brain tissues [33,34], it can be noninvasive and play a beneficial role in increasing ATP biosynthesis and neurogenesis [1,2]. A number of excellent reviews have focused on LLLT for TBI [1-3,35], depression [36] and AD [35,37].

Increasing evidence supports roles for LLLT in rodent models of TBI [1,35]. 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 model of TBI [24,25,28-32]. In addition, the clinical studies found that LLLT could improve cognition and decrease depression, anxiety, headache and insomnia in patients with chronic

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TBI [26,27]. Thus, LLLT could be an alternative approach for treatment of TBI.

Depression is a common mental disorder characterized by depressed mood, slow thought, diminished volitional activity, cognitive decline and somatic symptoms [38]. Recently, Xu et al. investigated that LLLT effectively decreased depression-like behaviors; it also increased ATP biosynthesis and the level of mitochondrial complex IV expression and activity in two depressive-related mice models [4]. The two mice models were space restriction and Abelson helper integration site-1 (Ahi1) knockout (KO) mice [4]. In another study using forced swimming test (FST) and electrocorticography (ECoG) spectral analysis, transcranial LLLT was shown to successfully ameliorate depressive-related behavior induced by reserpine in rats [5]. Further, LLLT could enhance outcomes for treatment of depression in clinical studies [6-8]. These results were summarized in **Table 1**. Collectively, this data suggest that transcranial LLLT has a beneficial role in depressive–related behaviors.

AD, which is a chronic neurodegenerative disease, is characterized by a progressive decline in many cognitive functions, resulting in memory loss and dementia [39]. Extracellular accumulation of amyloid β (Aβ) peptide aggregates, which results in the formation of senile plaques, indicates one of the neuropathological markers of AD [39]. In recent years, accumulating evidence has suggested that transcranial LLLT suppresses Aβ-induced hippocampal neurodegeneration and long-term spatial and recognition memory impairments in rats that were injected bilaterally with Aβ 1-42 to the hippocampus CA1 region [9]. Moreover, LLLT also inhibited Aβ 25-35-induced pheochromocytoma (PC12) cell apoptosis [20]. Furthermore, laser irradiation with moderate levels of 670-nm light and epigallocatechin gallate (EGCG) supplementation complementarily decreased Aβ aggregates in human neuroblastoma (SH-EP) cells [18]. More detailed information was summarized in **Table 2**. Taken together, LLLT plays beneficial roles in AD.

The mechanisms of LLLT in depression LLLT might increase the levels of brain monoamine neurotransmitters

Depression is a common mental disorder. Studies have shown that the specific symptoms of depression in adults are closely related to three major monoamine neurotransmitters in the brain circuits including dopamine, serotonin and norepinephrine [38]. The pathogenesis of depression is largely neurotransmitter-dependent. Serotonin is a messenger that produces pleasure and affects almost every aspect of brain activity from regulating emotion, energy, and memory to shaping life [38]. Therefore, antidepressants generally play a role by increasing brain serotonin [40]. In addition, dopamine is also an important neurotransmitter which is closely related to depression, mainly used to transmit excitement and happiness [40]. Both serotonin and dopamine levels in the

Table 1: Summary of studies on LLLT for treatment of depression.

Subjects	Wavelength of laser	Power output density of laser	Duration of laser irradiation	LLI treatment effects	References
Male adult ICR mice	808 nm	23 mW/cm^2	30 min per day for 28 days	Improved depression-like behaviors; elevated ATP biosynthesis and the level of mitochondrial complex IV expression and activity in PFC	[4]
Adult male albino rats	804 nm	approximately 0.64, 1.60, and 3.18 W/cm^2	1 min	Significantly decreased animal's immobility in the FST; increased significantly delta frequency band in ECoG spectral analyses	[5]
10 patients with major depression	810 nm	250 mW/cm^2	4 min	Reductions in both HAM-D and HAM-A scores; No side effects.	[6]
39 sequential patients with depression	810/980 nm	55-81 J/cm^2	9–12 min	Deduction of QIDS total score	[7]
51 adults with de-pression	1064nm	250 mW/cm^2	4 min	Greater symptom improvement among participants whose attention was responsive to ABM	[8]

ABM: attention bias modification; ATP: adenosine triphosphate; ECoG: electroencephalographic; FST: forced swimming test; HAM-A: a Hamilton Anxiety Rating Scale; HAM-D: a Hamilton Depression Rating Scale; ICR: Institute of Cancer Research; LLI: low-level laser irradiation. PFC: prefrontal cortex; QIDS: the Quick Inventory of Depression Symptomatology-Self Report;

Table 2: Summary of studies on LLLT for treatment of Alzheimer's disease.

Subjects	Wavelength of laser	Power output density of laser	Duration of laser irradiation	LLI treatment effects	References
Male Sprague-Dawley rats	808 nm	25 mW/cm² (cerebral cortex tissue); 8.33±0.27mW/cm² (hippocampus tissue)	Two-minute daily for 5 consecutive days	Suppress A_{β}-induced hippocampal neurodegeneration and long-term spatial and recognition memory impairments	[9]
The Aβ PP transgenic mouse model of Aβ peptide amyloidosis	808±10 nm	~10 mW/cm²	1 min	An increase in soluble AβPP; an increase in ATP levels , mitochondrial function and c- fos; reduction in expression of inflammatory markers	[10]
Male and female TASTPM mice	1072 nm	5 mW/c^{m}2	6 min	Reduction in Aβ $_{1-42}$ plaques in the cerebral cortex	[11]
APP/PS I and K3 tau transgenic mouse	670 nm	2m W/cm²	90 s	Mitigating degeneration in many regions of the mouse brain	[12]
30 femalemice from CDl mice	1072 nm	Not found	6 min	Improved cognitive performance	[13]
PC12 cells 0.52 mW/cm2	632.8 nm	0.52 mW/cm²	From 5 to 40 mins	Inhibited A Aβ $_{25-35}$ induced PC 12 cell apoptosis	[20]
PC12 cells	632.8 nm	12.74 mW/cm²	Not found	Increased the nuclear translocation of -catenin and enhanced its T cell factor/ lymphocyte enhancer factor-dependent transcriptional activity	[17,18]

hippocampus were significantly down-regulated in Ahi1 KO mice, which reveals depressive-like behaviors [4]. Transcranial LLLT attenuated depressive-like behaviors in Ahi1 KO mice, which could be involved in the enhancement of serotonin and dopamine levels in the brain [4]. Thus, the therapeutic mechanism of LLLT on depression is closely associated with monoamine neurotransmitters **(Figure 1)**.

■ LLLT enhances ATP biosynthesis

Depression, which is characterized by lack of energy, impaired concentration and fatigue, is believed to be closely related to mitochondrial dysfunction [40-42]. These clinical symptoms may be partly attributed to reduced synthesis of adenosine triphosphate (ATP) due to mitochondrial dysfunction [41-43]. ATP, which is produced by mitochondria, is the main source of cellular energy. Energy is conserved via the mitochondrial respiratory chain as the so-called proton motive force. Transcranial LLLT promotes ATP biosynthesis and increases the expression level and activity of mitochondrial complex IV in mice prefrontal cortex in depressive mouse model [4]. To support this idea, Ferraresi et al. illuminated that LLLT increases mitochondrial membrane potential and ATP synthesis in C2C12 myotubes [44]. Therefore, the therapeutic mechanism of LLLT on depression may be associated with an increase of ATP-production caused by low-level laser irradiation (LLLI) **(Figure 2)**.

■ The mechanisms of LLLT in AD LLLT contributes to mitochondrial homeostasis in AD

Although the pathogenesis of AD remains unclear, it has been widely recognized that AD is characterized by extracellular Aβ plaque and neurofibrillary tangles within neurons [39]. A large number of studies show that the development process and the pathogenesis of AD are closely related to a series of pathological processes including intracellular neurofibrillary tangles, oxidative stress, nerve inflammation and mitochondrial dysfunction with consequent neuronal dysfunction and cell death [39]. Lu Y et al. illuminated that Aβ injection into the hippocampus led to mitochondrial abnormalities including impaired mitochondrial dynamics and mitochondrial fragmentation [9]. In contrast, transcranial LLLT is able to shift mitochondrial dynamics toward fusion by balancing the mitochondrial targeting fission proteins and

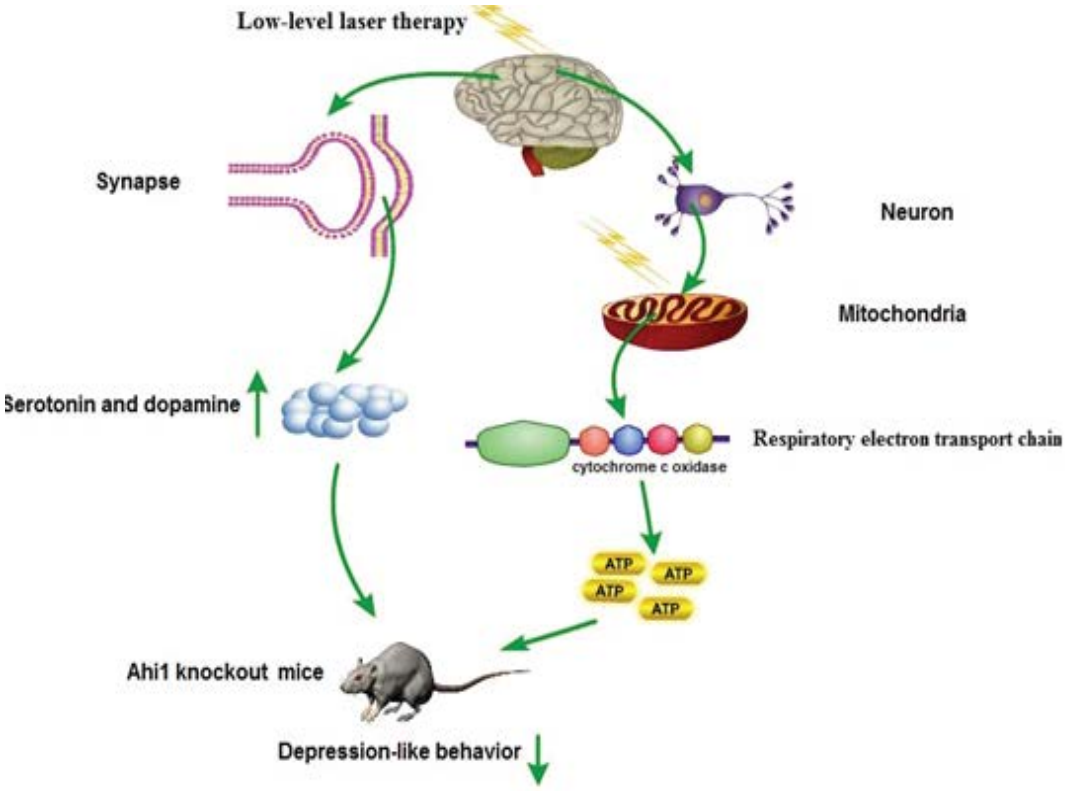

Figure 1: The mechanisms of LLLT in depression.

Light passes through the scalp and the skull, whereupon it is absorbed by cytochrome c oxidase in the mitochondrial respiratory chain of the cortical neurons. Adenosine triphosphate (ATP) biosynthesis is increased as a result of stimulated mitochondrial activity. LLLT might increase the secretion of monoamine neurotransmitters in the brain of Ahi 1 knockout mice. These monoamine neurotransmitters include serotonin and dopamine.

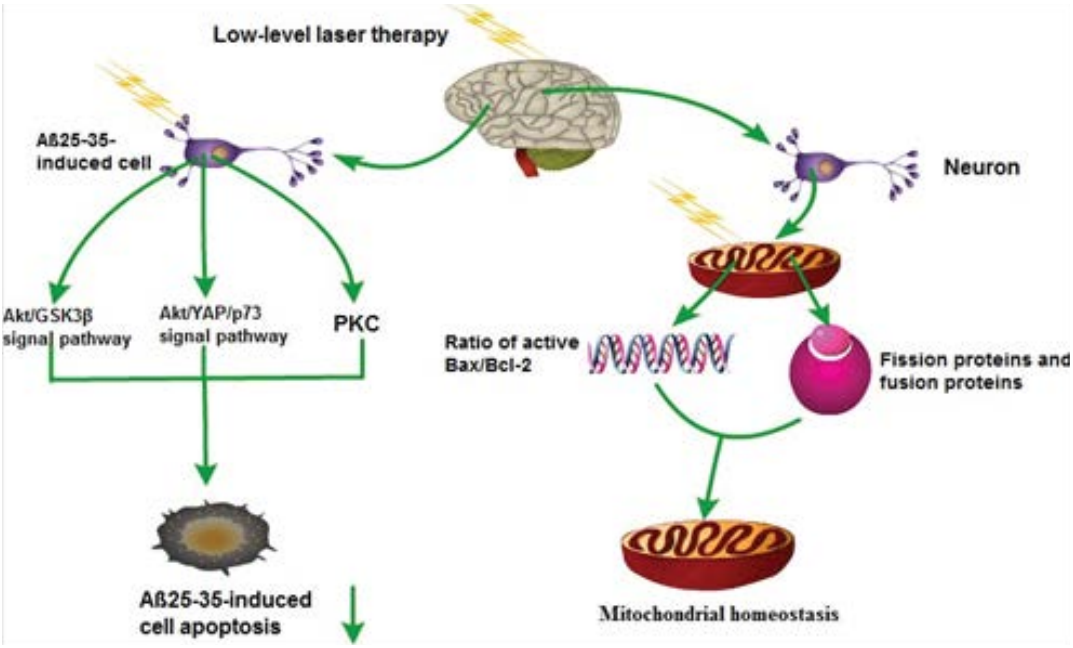

Figure 2: The mechanisms of transcranial LLLT on Alzheimer's disease.

Light passes through the scalp and the skull, whereupon transcranial LLLT shifts mitochondrial dynamics toward fusion by balancing the mitochondrial targeting fission and fusion proteins. LLLT regulates/modulates the mitochondrial targeting ration of active Bax/Bcl-2. LLLT colud inhibit $A\beta_{25\text{-}35}$ induced cell apoptosis by Akt/YAP/p73/GSK3β/PKC.

fusion proteins [9]. Simultaneously, LLLT regulates the mitochondrial targeting ratio of active Bax/Bcl-2 and antioxidant level, intimating a vital role of LLLT in facilitating mitochondrial homeostasis and protection in hippocampal CA1 neurons [9]. Collectively, the mechanism of LLLT in the treatment of AD is closely related to mitochondrial homeostasis [42,45].

■ LLLT is involved in regulation of oxidative stress and anti-inflammation

Heat shock protein (HSP) signaling pathways are involved in AD [46]. HSP reduction may lead to insufficient levels available to regulate abnormal polypeptide folding and processing, resulting in toxic accumulation which can initiate the apoptotic pathway, and may contribute to the progression of AD [47]. Consistent with idea, Grillo et al examined whether LLLT upregulates HSP and reduces the aggregation of Aβ in TASTPM mice, a mouse model of AD [11]. They found that LLLT treatment upregulates HSP, which reduce Aβ protein aggregation and neuronal apoptosis [11]. The data suggest that LLLT treatment may regulate oxidative stress to combat AD [11].

Inflammation is responsible for the pathophysiology of AD. De Taboada et al tested whether LLLT plays an anti-inflammation role in an Aβ protein precursor (AβPP) transgenic mouse model, a mouse model of AD [10]. They found that LLLT treatment decreases Aβ plaques and the expression of inflammatory markers in the AβPP transgenic mice [10]. In addition, LLLT treatment showed an increase in ATP levels, mitochondrial function, and c-fos, which result in an overall improvement in neurological function [10]. The data suggest that LLLT is a potential candidate for treatment of AD.

■ LLLT regulates/modulates multiple intracellular down-stream signaling pathways in AD

Although the molecular mechanism of LLLT in the treatment of AD is highly complex, increasing number of studies using LLLT was found recently. Zhang et al. have reported that Aβ 25-35 can induce pheochromocytoma (PC12) cell apoptosis by increasing the level of bax mRNA, and the anti-apoptotic effect of LLLT is dependent on the up-regulation of bclxl and down-regulation of bax via protein kinase C (PKC) activation pathway [20]. Moreover, LLLT increased the nuclear translocation of β-catenin and enhanced its T cell factor/lymphocyte enhancer factor-dependent transcriptional activity via the Akt/GSK3β pathway to promote cell survival upon treatment with Aβ 25-35 [19]. LLLT has a prosurvival effect on Aβ-induced apoptosis and may be an effective therapeutic strategy in treating AD by targeting GSK3b [17]. In addition, another study on EGCG has also found that irradiation with moderate levels of 670-nm light and EGCG supplementation complementarily reduces Aβ aggregation in human neuroblastoma SH-EP cells [18]. Further, Zhang et al. has uncovered evidence that LLLT could inhibit Aβ 25-35-induced cell apoptosis through activation of Akt/Yes-associated protein (YAP)/p73 signaling pathway [19]. Taken together, these results directly point to a potential therapeutic strategy for the treatment of AD through Akt/YAP/p73/GSK3β/PKC signaling pathways with LLLT (Fig. 2). Interesting, a recent study by Iaccarino et al demonstrated that entraining gamma oscillations (20 to 40 Hz), which is different from LLLT, may provide systemic effects in the brain to attenuate AD-related pathology through modulation of microglia [48]. Further study in gamma oscillations and LLLT is warranted to examine whether it will have therapeutic effects in human AD.

Conclusion and Perspective

As a noninvasive treatment, accumulating evidence has shown that transcranial LLLT is a beneficial treatment for depression [4,5] and AD [10-17] in rodent models. In addition, transcranial LLLT has been carried out on depression and chronic TBI patients in preclinical trials [6-8,26,27]. With the increasing enthusiasm for studies on LLLT, the cellular and molecular mechanisms of LLLT are still at early stages. LLLT might be related to factors such as mitochondrial oxidative respiratory chain, Akt/YAP/p73/GSK3β/PKC signaling pathway, and neurogenesis, neuroplasticity, and monoamine neurotransmitters as mentioned above. However, the main mechanism of LLLT is closely related to the function of mitochondria in pathophysiological conditions [1,45]. Mitochondria might be the most important organelle within cells governing the LLLT responses [1,42].

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 model [46], LLLT, as

a new therapeutic technology, needs more studies to prove its safety. In addition, we need to examine the effects of LLLT including laser wavelength, energy intensity, irradiation mode, and the duration of laser on physiological and pathological conditions. Further, we should explore other cellular and molecular mechanisms responsible for its effect. Most importantly, it is critical to test the effects of transcranial LLT in treatment of depression and AD in clinical trials. In conclusion, transcranial LLLT will shed new light on the treatment of psychological and neurological disorders.

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