Journal of
Bioengineering & Biomedical Science

Salgado et al., J Bioengineer & Biomedical Sci 2015, 5:1
DOI: 10.4172/2155-9538.1000144

Research Article Open Access

Transcranial Light Emitting Diode Therapy (TCLT) and its Effects on Neurological Disorders

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Abstract

The Transcranial LED Therapy (TCLT) is a modality of low-level energy therapy based on the principle of photons delivered in a non-invasive manner for the rehabilitation of some neurological conditions such as psychological disorders, traumatic brain injuries, and neurodegenerative diseases among others. Because the phototherapy approach has attracted interest in the scientific medical field we discuss the action of TCLT at the cellular level in this review. Cytochrome c oxidase is the main target of TCLT for therapeutic effects by enhancing cerebral blood flow. This enzyme boosts cell respiration and energy production, which induces cell proliferation and reduces apoptosis in Alzheimer and Parkinson's diseases. Thus, TCLT is a safe, non-invasive, and low cost alternative treatment compared to other treatment modalities for clinical neurological disorders.

Keywords: Transcranial light emitting diode therapy; LED; Neurodegenerative disease; Cytochrome oxidase

Introduction

The brain suffers a wide variety of anatomical and functional alterations during normal aging associated with an increased risk of neurovascular age-related changes that compromise the functional integrity of the neurological system, which can lead to neurodegenerative diseases [1]. Cerebral blood flow (CBF) and continuous cerebral perfusion are vital for neural function, and thus, are considered important indicators of brain health. Reduction and disruption in the CBF have been associated with numerous disease conditions such as hypertension, ischemic stroke, and dementia related diseases such as Alzheimer's disease (AD) [2]. Regional hypoperfusion is associated with an accumulation of amyloid [3,4] and cognitive impairment [5].

The effects of phototherapy on CBF have been demonstrated including those produced by light emitting diodes (LED). One of the main mechanisms of action of TCLT (Transcranial LED therapy) is potentially the prevention of neurons death, hypoxia, trauma, or toxicity [6] by upregulating the production of cytoprotective genes such as those encoding antioxidant enzymes and anti-apoptotic proteins. In AD, the presence of the β-amyloid peptide can trigger the formation of reactive oxygen species and nitrogen (ROS) that induce lesions in mitochondria, which in turn, lead to neurons synaptic loss and cell death [7], which are also observed in other neurodegenerative diseases [7,8].

Researches show that radiation in the red region of the electromagnetic spectrum is absorbed by the cytochrome c oxidase in the mitochondrial respiratory chain [9] leading to increased cellular respiration, ATP synthesis, and increased proliferation of nerve cells [10] among others. However, few studies analyzed the efficacy of TCLT in relation to cerebral blood and vascular circulation in humans and its correlation with pathological states, age ranges, and functional conditions. Thus, this review examined studies concerning the effects of TCLT on neurodegenerative diseases.

Overview of the Use of LED in Medical Science

The use of light as a therapeutic tool (the generic term is phototherapy) has been documented in the medical literature since 1500 B.C. The use of light for therapeutic implications involves only a small portion of the total electromagnetic radiation spectrum characterized within 630-1000 nm (red to near-infrared) [11,12]. Since the advent of phototherapy in the field of medical science, a wide variety of light sources have being evaluated. The effects of radiation (i. e. red and near-infrared) on tissues and cells have been studied by physicists initially using low-intensity lasers and later LED [13]. Thus, researchers have demonstrated the applicability of therapeutic red/near-infrared LED in the treatment of a range of diseases and injuries after the observation of the benefits promoted by LED in astronauts in the space.

This type of light source has advantages over laser because it is relatively less expensive, its diode can be configured to produce multiple wavelengths allowing diffuse light radiation over large surface areas, it does not produce heat, it requires less energy, and is considered safe by the FDA (Food and Drug Administration).

The therapeutic use of LED in the red to near-infrared wavelengths is also characterized by relatively low energy density. In addition to its beneficial effects observed on a variety of clinical conditions, much attention has been currently given to the satisfactory results observed on functional and structural brain injuries such as traumatic brain injuries resulting in behavioral, cognitive, and biochemical changes [14,15]. Significant results were seen when TCLT was applied to patients suffering from depression and anxiety [16], in neurodegenerative diseases such as Parkinson's and Alzheimer's diseases experimentally induced in rats [17,18], and in cerebral blood flow disruption [19]

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Received: December 19, 2014; **Accepted:** March 10, 2015; **Published**: March 17, 2015

Citation: Salgado SIA, Parreira RB, Ceci LA, de Oliveira LVF, Zangaro RA (2015) Transcranial Light Emitting Diode Therapy (TCLT) and its Effects on Neurological Disorders. J Bioengineer & Biomedical Sci 5: 144. doi:10.4172/2155- 9538.1000144

among others. Table 1 shows a summary of studies about the effects of TCLT and the parameters used.

Transcranial light emitting diode therapy (TCLT)

The mitochondrial function in events such as ischemia, neurotoxicity, and cell repair and the effects of phototherapy on affected brain regions have been researched for some time. Neurodegeneration and some brain functions, such as memory, are very sensitive to the inhibition of cytochrome oxidase and the energy deficit associated with aging and cerebral perfusion impairment [20]. Some studies show that increased CBF, specified in the parietal and frontal lobes in humans, significantly improve psychological performance in patients with psychological disorders, traumatic brain injuries, and neurological disorders such as Alzheimer and Parkinson's diseases (Table 1).

The results suggest improvements that can be categorized in three areas.

1 – Improved brain function in the prefrontal cortex and anterior cingulate gyrus region. These areas are responsible for monitoring, maintaining, and manipulating information in the working memory and sustaining attention [21,22]. Rojas et al. conducted a study with rats submitted to behavioral experiments (extinction and renewal effects). These authors concluded that the rats had enhanced extinction memory, prevented the reemergence of extinguished conditioned fear responses, and showed a reduced fear renewal after TCLT. In humans, Schiffer et al. showed that one single TCLT session applied to the skull (frontal region) resulted in increased (CBF) and significant improvement in the treatment of major depression and anxiety.

2 – *In vivo* photobiostimulation can promote increased mitochondrial respiration and metabolic capacity in the brain. This effect involves a neuroprotective action [23-25] and an increased production of nitric oxide (NO) and CBF in mice [26]. Photobiostimulation increases the utilization of oxygen and NO production through cytocrome oxidation and may protect against cerebral hypoperfusion. Poor perfusion is a condition that occurs in some neurological conditions and in elderly people. Salgado et al. verified the effects of TCLT on CBF in elderly women by transcranial Doppler ultrasound. The authors showed that left and right middle cerebral arteries and the basilar artery showed increased CBF after TCLT delivered in the front and parietal cranial regions. A previous study showed a rise in CBF after one single session of TCLT.

3 – TCLT can prevent neurodegenerative diseases through the activation of transcription factors involved in the expression of many protective factors such as antioxidants and anti-apoptotic factors [27]. These effects are demonstrated in a study by Hanczyc et al. [28]

Author	Study type	Model	Condition	Protocol	Results
Schiffer et al., [16]	Pilot study	Human	Depression and anxiety	LED 810nm; PD=250 mW/cm^2; ED=60 J/cm^2, 4 min.	Significant results on HAM-A 2nd e 4th week treatment; on 2nd week symptoms remission in 6 of 10 patients.
Naeser et al., [15]	Case study	Human	Traumatic brain injury	LED 870nm; Total power=500mW PD=25.8 mW/cm^2; ED=1 J - 2 s, 1 J/cm^2 - 38.8 s.	Improvement in cognition.
Nawashiro et al., [26]	Case study	Human	Vegetative state CBF	LED 850nm; PD=1.14 W/cm^2; ED=20.5J/cm^2; 30 min;	Increase in CBF (20%) and Improved neurological condition from the 6th day.
Naeser et al., [15]	Protocol study	Human	Severe and mild Traumatic brain injury	LED - 633nm, and 870 nm PD=13 J/cm^2; ED 22.2 mW/cm^2	Improved sleep, fewer post-traumatic stress disorder Symptoms. Better social, occupational and interpesonal functions.
Duan et al., [18]	Experimental	*In vitro*	β-amyloide	LED 640 ± 15nm; PD=0.5 to 10W/cm^2; T=30 a 60 min.	LED significatly decreased apoptosis induced β-amyloide.
Quirk et al., [14]	Experimental	Animal	Traumatic brain injury	LED 670 nm; PD=50mW/cm^2; ED=15J/cm^2; 5 min.; for 10 days.	Improves the recovery process after head injury; significant decrease of Bax e Bcl-2.
Salgado et al., [19]	Clinical	Human	Cerebral blood flow	LED 627 nm; PD=70 mW/cm^2; ED=10J/cm^2	TCD parameters showed significant improvement in the blood flow on the arteries analyzed
Liang et al., [17]	Experimental	*In vitro*	Neurotoxicity	LED 670 nm; PD=50mW/cm^2; ED = 4 J/cm^2; 80 seconds, 2 times/day	cellular ATP increased significantly and reduced neuronal death. LED protected nerves cell from toxins related to Parkinson's disease.
Wong-Riley et al., [23]	Experimental	*In vitro*	Neurotoxicity	LED 670, 728, 770, 830, 880 nm; PD=50 mW/cm^2; ED=4 J/cm^2; applied for 1 min and 20 sec.	Wavelengths 830 and 670 nm was the most effective in the NIR absorption spectrum of Cco.
Rojas et al., [20]	Experimental	Animal	Cognitive functions Oxygen consumption	LED 660 nm; DP=9 mW/cm^2 ED=9, 10.9, 21.6, 32.9 J/cm^2	TCLT increased prefrontal cortex oxygen consumption; was able to facilitate fear extinction memory at 10.9 Jcm$^{/2}$, prevented fear renewal and increased the metabolic capacity of the prefrontal cortex
Moro et al.,	Experimental	Animal	Parkinson's disease	LED=670 nm; PD=5.5 mW/cm^2; ED=2 J/cm^2;	Neuroprotective benefits at both cellular and behavioural levels

Note: LED=light emitting diode; PD=power density; ED=energy density; HAM-A=Hamilton Anxiety Rating Score; NIR=near-infrared; CBF=cerebral blood flow; Aβ=beta-amilase; ROS=reactive oxigen species; VEGF=vascular endothelial growth factor; MAPK=mitogen-activated protein kinase; Cco=cytochrome c oxidase; TDC= transcranial Doppler ultrasound; TLTC=trasncranial led therapy.

Table 1: Summary of LED articles on neurological conditions.

showing that amyloid fibrils, which include the β-amyloid, have great absorption capacity of photons emitted in the 650-930 nm range due to the presence of chromophores in their molecular structure; this structure can be damaged according to the absorbed energy.

Duan et al. used LED (640 ± 15 nm) in cultured cells and observed a significant reduction in apoptosis induced by β-amyloid. According to Yang et al. [29], the inhibition of ROS production after low-energy laser therapy reduced the formation of β-amyloid and presence of astrocytes, and induced post-trauma nerve regeneration. The results of our experiments [in revision for publication] showed a reduction in glial cells and senile plaques in the brains of rats after 21 days of TCLT compared with untreated rats in the control group.

These benefits are mainly mediated by the bioenergetics effects of mitochondria on cytochrome oxidase in the brain as demonstrated in *in vivo* experiments showing induced up-regulation of cytochrome oxidase in the cortex after TCLT. It is assumed that the effect of TCLT over cytochrome oxidase reverses the consequences of cerebral hypo perfusion through the vasodilator effect of NO that results in increased oxygen consumption and, thus, improved neuronal respiration.

Biological effects of TCLT

Low power photostimulation can modulate many cellular processes in biological tissues. In the transcranial modality, TCLT acts directly on the brain tissue generating significant effects of stimulation and proliferation, release of chemical mediators, regulation of cellular processes, and improvement of energy metabolism in mitochondria among others [30]. The basic principle of TCLT is to stimulate brain cells through photons that are absorbed primarily by the mitochondrial respiratory enzyme, thus resulting in increased basic energy processes in each photo stimulated cell, i. e., acceleration of electron transfer in the respiratory chain, activation of the cytochrome c oxidase system and increase in cellular ATP production.

The mechanism proposed by TCLT is that phototherapy stimulates the cytochrome *c* oxidase increasing the usage of oxygen in the brain and its metabolic capacity; these effects would increase brain function and protect against neurological deficits such as those caused by cerebral vascular hypoperfusion. However, other possible mechanisms may be involved in intra, inter-, and extracellular biological events. Thus, there is a growing body of evidence suggesting that the primary effects of TCLT would be the photo stimulation of mitochondrial cytochromes, which may initiate secondary cell-signaling pathways [31,32] producing desirable effects. It is well known that there is a high concentration of mitochondria in the brain, which is responsible for several functions. Therefore, some pathologies such as neurodegenerative diseases can lead to mitochondrial dysfunction that impairs the energy supply in the brain.

Some researchers have investigated the effects of cytochrome oxidase and TCLT on brain functions. Rojas et al. reported that TCLT induces brain metabolic and antioxidants effects through the analysis of cytochrome oxidase increases. In another study, these authors reported an increase in memory retention and oxygen consumption over cytochrome oxidase stimulation in the frontal cortex of rats. Thus, mitochondria would be the prime target of TCLT because they because they display the highest potential as a photo acceptor and because of their crucial role in supplying energy to cells.

Cytochrome *c* oxidase as a primary photoacceptor

The three major photoacceptors in the red/near-infrared wavelength range are hemoglobin, myoglobin, and cytochrome *c* oxidase. Cytochrome *c* oxidase is the only one to produce energy, displays the greatest potential as a neuronal photoacceptor in the red to near-infrared light range [33], and is a marker of neuronal energy metabolism. Cortical neurons are extremely rich in mitochondria and believed to be the origin of the transducing effects of mitochondria radiation to other neural components such as cytoplasm, cell membrane, and the nucleus [34]. Thus, the process of photo transduction can occur after light exposure, which activates several intracellular metabolic and enzymatic pathways and is considered responsible for the TCLT effects.

Cytochrome *c* oxidase is an enzyme that catalyzes the final step in the mitochondrial respiratory chain when an electron from each of the four cytochrome *c* molecules is transferred to an oxygen molecule, converting into two water molecules. Protons across the mitochondrial inner membrane will be released in this process allowing the formation of adenosine triphosphate (ATP) by oxidative phosphorylation [35]. The cytochrome *c* has two copper centers (the CuA and CuB), where the electrons admitted CuA of cytochrome *c* in the process of mitochondrial respiration chain [36], where the absorption of light occur, mainly in the red/near-infrared spectrum.

TCLT acts as an exogenous source of highly energized electrons for the respiratory chain, thereby promoting endogenous donation of electrons, for example in NADH and FADH2, enhancing the cellular energy metabolism [37,38]. Photo stimulation can restore the flow of electrons when the entry of these electrons is blocked in the respiratory chain as it occurs in neurodegenerative diseases. Indeed, it is also possible that phototherapy can maintain the cellular membrane potential in mitochondria, reduce the reverse passage in the electron transport chain, and increase ATP synthesis, which results in a reduction in the release of free radicals, by increasing the flow of electrons in the electron transport chain .Thus, TCLT facilitates the activity of cytochrome *c* oxidase accelerating the transfer of electrons in the mitochondrial inner membrane and boosting cell respiration and energy production.

The primary effects of radiation depend on the absorption of light by mitochondria; the cytochrome *c* oxidase respiratory enzyme is considered the greatest photo acceptor of light in the red/near-infrared wavelength range. Karu et al. demonstrated that cytochrome *c* oxidase has four absorption peaks in the red/near-infrared spectrum; these authors revealed that the photo acceptor was characterized as with relatively low intensity in the 710-790 nm wavelength range, while it was characterized as a relatively oxidized photoacceptor in the 650-680 nm wavelength range featuring the redox state of cytochrome *c* oxidase. CuA contains a broad peak of wavelength absorption when oxidized, thereby allowing noninvasive penetration into the brain. Riley-Wong et al. also showed that 670 nm was the most effective wavelength to reverse the effects of the cytocrome *c* oxidase inhibitor (potassium cyanide - KCN) and suppress the neurotoxic effects promoted by tetrodotoxin, protecting nerve cells from cell death. Therefore, the cytochrome *c* oxidase acts as the main cellular component for photon absorption in the red/near-infrared wavelength range, which would be responsible for triggering many biological and biochemical processes. This function can result in an improvement in energy metabolism and cellular viability, prevention of cell apoptosis in an ischemic event, and enhancement of neuronal repair mechanisms.

TCLT radiation transmission in the skull

Few studies have evaluated the transmission rate of the red/near-infrared radiation in the skull. Wan et al. [39] observed that radiation

Biological tissue			
	White	Gray	Skull
Study	**Parameter**	**matter**	**matter**
Simpson et al. [42]	μa [mm-1]	0.003-0.01	0.032-0.038
	μ_s [mm-1]	9.26-7.78	2.64-2
Firbank et al. [41]	μ_a [mm-1]		0.02-0.05
	μ_s [mm-1]		35-25

Table 2: Optical absorption and scattering coefficient in the human brain.

emitted in the 600-800 nm spectrum can penetrate about 1 cm in the skull of human cadavers. Jagdeo et al. [40] showed that this radiation range can penetrate soft tissues, bone, and brain parenchyma in a study using cadavers preserved in formalin. According Firbank et al. [41], the absorption coefficient of radiation in the 650 nm and 950 nm range is between 0.02 and 0.05 mm^{-1} in the skull, while the scattering coefficient has a linear decrease from 35 mm^{-1} at 650 nm wavelength to 25 mm^{-1} at 950 nm wavelength. Similarly, the absorption and scattering coefficients of brain white and gray matter for the same region of the spectrum do not differ greatly [42]. Table 2 describes the radiation absorption and scattering coefficients in different human biological tissues.

These data show that, in this wavelength range, the variations in absorption and scattering coefficients are not extreme, and therefore, a model for the near-infrared region does not significantly differ from the model for the red region. In addition, scattering coefficients are higher than absorption coefficients; absorption coefficients are practically negligible when the Beer-Lambert law is applied.

Haeussinger et al. [43] determined that the amount of radiation absorbed by the brain gray matter is in the order of 3% when a certain amount of radiation is applied to the scalp. Naeser and Hamblin advocated that red/near-infrared photons can penetrate deeply into the skull and reach the cortex. Therefore, photons could penetrate small vessels that supply arterial blood to the superficial areas of the cortex, including areas away from the site of irradiation. Salgado et al. demonstrated this effect when effects were observed over the basilar artery after TCLT was applied in the frontal and parietal regions of the skull.

Thus, as demonstrated in this review, we can infer that a small amount of energy is sufficient to produce such effects and that this type of phototherapy is safe and shows little or no side effects.

Conclusion

TCLT is a cost-effective, safe, and non-invasive alternative treatment for neurological clinical conditions such as Alzheimer's and Parkinson's diseases, dementia, psychological disorders, stroke, and cranial traumatisms. Furthermore, because red/near-infrared light can penetrate the brain at low energy doses, TCLT could be extensively used in non-invasive treatments with no negative side effects.

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