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Neurological and psychological applications of transcranial lasers and LEDs.

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Abstract

Transcranial brain stimulation with **low-level** light/**laser therapy** (LLLT) is the use of directional **low**-power and high-fluency monochromatic or quasimonochromatic light from lasers or LEDs in the red-to-near-infrared wavelengths to modulate a neurobiological function or induce a neurotherapeutic effect in a nondestructive and non-thermal manner. The mechanism of action of LLLT is based on photon energy absorption by cytochrome oxidase, the terminal enzyme in the mitochondrial respiratory chain. Cytochrome oxidase has a key role in neuronal physiology, as it serves as an interface between oxidative energy metabolism and cell survival signaling pathways. Cytochrome oxidase is an ideal target for cognitive enhancement, as its expression reflects the changes in metabolic capacity underlying higher-order brain functions. This review provides an update on new findings on the neurotherapeutic applications of LLLT. The photochemical mechanisms supporting its cognitive-enhancing and brain-stimulatory effects in animal models and humans are discussed. LLLT is a potential non-invasive treatment for cognitive impairment and other deficits associated with chronic neurological conditions, such as large vessel and lacunar hypoperfusion or neurodegeneration. Brain photobiomodulation with LLLT is paralleled by pharmacological effects of **low**-dose USP methylene blue, a non-photic **electron** donor with the ability to stimulate cytochrome oxidase activity, redox and free radical processes. Both interventions provide neuroprotection and cognitive enhancement by facilitating mitochondrial respiration, with hormetic dose-response effects and brain region activational specificity. This evidence supports enhancement of mitochondrial respiratory function as a generalizable therapeutic principle relevant to highly adaptable systems that are exquisitely sensitive to energy availability such as the nervous system.

KEYWORDS: Cognitive enhancement, Cytochrome oxidase, **Low-level** light **therapy**, Methylene blue, Neuroprotection, Photobiomodulation

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Role of Low-Level Laser Therapy in Neurorehabilitation

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Abstract

This year marks the 50th anniversary of the discovery of the laser. The development of lasers for medical use, which became known as low-level laser therapy (LLLT) or photobiomodulation, followed in 1967. In recent years, LLLT has become an increasingly mainstream modality, especially in the areas of physical medicine and rehabilitation. At first used mainly for wound healing and pain relief, the medical applications of LLLT have broadened to include diseases such as stroke, myocardial infarction, and degenerative or traumatic brain disorders. This review will cover the mechanisms of LLLT that operate both on a cellular and a tissue level. Mitochondria are thought to be the principal photoreceptors, and increased adenosine triphosphate, reactive oxygen species, intracellular calcium, and release of nitric oxide are the initial events. Activation of transcription factors then leads to expression of many protective, anti-apoptotic, anti-oxidant, and pro-proliferation gene products. Animal studies and human clinical trials of LLLT for indications with relevance to neurology, such as stroke, traumatic brain injury, degenerative brain disease, spinal cord injury, and peripheral nerve regeneration, will be covered.

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Research Report

Low-Level Light Therapy Improves Cortical Metabolic Capacity and Memory Retention

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Abstract. Cerebral hypometabolism characterizes mild cognitive impairment and Alzheimer's disease. Low-level light therapy (LLLT) enhances the metabolic capacity of neurons in culture through photostimulation of cytochrome oxidase, the mitochondrial enzyme that catalyzes oxygen consumption in cellular respiration. Growing evidence supports that neuronal metabolic enhancement by LLLT positively impacts neuronal function *in vitro* and *in vivo*. Based on its effects on energy metabolism, it is proposed that LLLT will also affect the cerebral cortex *in vivo* and modulate higher-order cognitive functions such as memory. *In vivo* effects of LLLT on brain and behavior are poorly characterized. We tested the hypothesis that *in vivo* LLLT facilitates cortical oxygenation and metabolic energy capacity and thereby improves memory retention. Specifically, we tested this hypothesis in rats using fear extinction memory, a form of memory modulated by prefrontal cortex activation. Effects of LLLT on brain metabolism were determined through measurement of prefrontal cortex oxygen concentration with fluorescent quenching oximetry and by quantitative cytochrome oxidase histochemistry. Experiment 1 verified that LLLT increased the rate of oxygen consumption in the prefrontal cortex *in vivo*. Experiment 2 showed that LLLT-treated rats had an enhanced extinction memory as compared to controls. Experiment 3 showed that LLLT reduced fear renewal and prevented the reemergence of extinguished conditioned fear responses. Experiment 4 showed that LLLT induced hormetic dose-response effects on the metabolic capacity of the prefrontal cortex. These data suggest that LLLT can enhance cortical metabolic capacity and retention of extinction memories, and implicate LLLT as a novel intervention to improve memory.

Keywords: Cytochrome oxidase, fear extinction, memory enhancement, mild cognitive impairment, mitochondrial respiration, neurotherapeutics, photobiomodulation

INTRODUCTION

Low-level light therapy (LLLT) with red to near-infrared light is a promising and novel neurotherapeutic intervention in animals and humans [1–3]. LLLT *via* light-emitting diodes (LEDs) or lasers uses low-energy irradiation that avoids ablative effects on tissues, yet such energy is high enough to modulate cell functions. LLLT has well-established beneficial effects in nervous tissue *in vitro* and *in vivo*, including enhancement of gene expression [4] and nerve regeneration [5], and protection against traumatic injury [6–8], ischemic damage [9–11], and neurodegeneration induced by mitochondrial dysfunction [12–16]. The mechanism of action of LLLT implicates light absorption by chromophores in the mitochondrial respiratory enzyme cytochrome oxidase (also called cytochrome *c* oxidase or cytochrome *a–a3*), which contains chromophores with high absorbance in the

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