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Research Report

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

Julio C. Rojas[a,b], Aleksandra K. Bruchey[a] and Francisco Gonzalez-Lima[a,*]
[a]*Department of Psychology, Pharmacology and Toxicology, University of Texas at Austin, Austin, TX, USA*
[b]*Department of Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center, Dallas, TX, USA*

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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

*Correspondence to: Prof. Dr. F. Gonzalez-Lima, University of Texas at Austin, 108 E. Dean Keeton Stop A8000, Austin, TX 78712, USA. Tel.: +1 512 471 5895; Fax: +1 512 471 5935; E-mail: gonzalez-lima@psy.utexas.edu.

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