

Guest Editorial*

The Potential of Light Therapy for Central Nervous System Injury and Disease

LIGHT AS A NEURO-RESTORATIVE and/or neuro-protective therapy for the treatment of injury and diseases of the central nervous system (CNS) is a novel concept that is rapidly gaining attention. The earliest reports on the use of light for the treatment of CNS injury were the pioneering experiments of Shimon Rochkind.^{1–5} Rochkind and colleagues used 780-nm wavelength laser irradiation in a number of models of spinal cord injury (SCI) and reported enhanced axonal sprouting and spinal cord repair. What was amazing about this research and hard for many people to accept was the claim that light applied transcutaneously could penetrate to the level of the spinal cord and alter the response of the spinal cord to injury.

My laboratory, in conjunction with Drs. Waynant and Ilev of the U.S. Food and Drug Administration, was the first to definitively show that light applied transcutaneously penetrates to the level of the spinal cord. In a series of experiments on anesthetized Sprague Dawley rats, a broadband light source was directed at the surface of the skin in the region of the low thoracic vertebral level. A smart, tissue-activated optical fiber probe attached to a spectrophotometer was inserted sequentially into tissue layers from the skin to the spinal cord and a transmission spectrum in the range of 500–1200 nm was collected at each layer.⁶ Analysis of the transmission spectra revealed that the penetration was highest through all tissue layers overlying the spinal cord and through blood between the 770- and 820-nm wavelengths. The peak transmission was at 810 nm. Further analysis showed 98% of 810-nm light was transmitted through water.⁷ For SCI my laboratory has shown that 810-nm light is an effective therapy in both dorsal hemisection⁷ and contusion⁸ rodent models. The noninvasive transcutaneous application of 810-nm light at the injury site caused a significant increase in the number of regenerating corticospinal tract axons and the length of axonal regrowth. Functional recovery was achieved with ladder crossing time and angle of hind paw rotation returning to baseline levels 9 wk post-injury. Light therapy (LT) significantly decreased the invasion of cells involved in secondary damage to the spinal cord, including macrophages/activated microglia and T lymphocytes from 48 h to 5 wk post-injury, and astrogliosis was reduced at early time points.⁷ LT acutely applied after SCI also resulted in a statistically significant suppression of pro-inflammatory cytokine and chemokine expression⁷ and in a

significant alteration in a subset of genes involved in the immune response, cellular proliferation, and growth factor receptors.^{9,10} These data provide evidence that light exerts specific ameliorative molecular effects on the response of cells in the CNS to traumatic injury leading to immunosuppression and alteration of the secondary injury response and progression of the injury process. Additionally, optical measurements in human cadavers revealed that 810-nm light penetrates to the level of the spinal cord (J.J. Anders; USUHS, unpublished results). Based on these data, 810-nm light is an effective wavelength for treatment of the CNS.

Recent studies in our laboratory and others have documented that 810-nm and similar (808-nm) wavelength light applied to the scalp readily passes through the skull and into the brain and is effective in treating injury to the brain. Transcranial laser therapy (TLT) applied either 4–6 h or 24 h after ischemic stroke in rats and rabbits^{11–13} caused a significant improvement in neurological score compared to control animals. Oron et al.¹⁴ demonstrated that noninvasive transcranial application of light irradiation improves short- and long-term behavioral function and reduces brain tissue loss after traumatic brain injury. In fact, LT was recently shown to be safe and effective for treatment of humans within 24 h of stroke onset¹⁵ and a 660 patient NEST-2 study showed similar safety outcomes and a trend toward efficacy.¹⁶ TLT holds promise for becoming the new gold standard therapy for acute, mild stroke.

Currently there is great interest in using TLT for neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS). These disorders are particularly attractive as candidates for TLT based on current evidence indicating the role of mitochondrial dysfunction and ATP depletion, oxidative stress, pro-inflammatory factors, and apoptosis among the cascade of events leading to neuronal death. Since light can alter mitochondrial function, oxidative stress, pro-inflammatory factors, and rescue injured and/or dying neurons, TLT is a potential therapy for neurodegenerative disorders. Using an *in vitro* model of PD,¹⁷ light was reported to significantly increase cellular ATP, decrease the number of neurons undergoing cell death, and significantly reduce the expression of reactive oxygen and reactive nitrogen species in rotenone- and

***Editor's Note:** We are pleased to present the third in a series of six Guest Editorials written by luminaries in their respective disciplines to be published in Volume 27 of *Photomedicine and Laser Surgery*.

MPP⁺-exposed rat striatal and cortical neurons. However, caution is needed when considering TLT for the treatment of neurodegenerative diseases because of their complex and progressive neuropathology. A recent publication on the use of LT on the SOD1 transgenic mouse model of ALS reported that a brief, statistically significant improvement in function occurred in the group that received LT.¹⁸ These data suggest that LT delays the onset of motor deficits. However, the benefit was short-lived, indicating that LT cannot alter the ongoing process of mitochondrial vacuolation and degeneration that ultimately disrupts the electron transport chain in this animal model of ALS. This pathological progression explains the loss of a beneficial effect from LT in advanced stages of the disease.¹⁸ In support of this theory, a series of *in vitro* experiments using cell lines bearing the mitochondrial DNA of PD patients have identified dysfunctional components of the mitochondrial electron transport chain, which is essential for the production of ATP. The dysfunction leads to defective use of oxygen by these models of PD disease progression, and several PD cell lines had seriously crippled oxygen utilization machinery in their mitochondria. These PD cell lines showed minimal response to LT, whereas PD cell lines with more intact oxygen utilization machinery were more responsive to LT (Dr. Patricia Trimmer, University of Virginia, personal communication). This reasoning may also apply to other neurodegenerative diseases. Recently, it was reported that LED pretreatment caused a much greater increase in cellular content of ATP in primary neurons grown in rotenone or MPP⁺ compared to neurons treated by light during the exposure to the neurotoxins.¹⁹ The authors concluded that this finding may have relevance to animal models of PD, and may indicate that the treatment would be most effective as a preventative therapy used in the early stages of Parkinsonian induction before symptoms appear.

A major research challenge for establishing light as an effective therapy for CNS injuries and disease is optimization of the time of application of light for a particular injury or disease process. Identifying the effective temporal windows could alter the course of the inflammatory process and the secondary injury cascades that accompany trauma and neurodegenerative diseases. Investigation of light interaction with the CNS holds great potential for light/energy therapeutics to become the standard therapy for many CNS injuries and diseases that currently have no effective treatments.

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