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Photobiomodulation in Light of Our Biological Clock's Inner Workings

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The 2017 Nobel Prize in Physiology or Medicine was awarded to J.C. Hall, M. Rosbash and M.W. Young, for being ''able to peek inside our biological clock and elucidate its inner workings.''[1] Ten years before, R. Lanzafame had argued that ''the application of physical forces at low energies and in certain repetitive frequencies can have profound effects on biological processes.''[2] That led us to submit a Letter to the Editor on the significance of physiological rhythms (PRs) and their potential modulation by external radiant energy in the photobiomodulation (PBM) range.[3] A decade later, new scientific evidence allows us to better understand both the importance of PRs, the negative connotations of their deregulation, as well as the means by which PBM might be able to help power and restore altered PRs to reestablish homeostasis-homeokinesis in higher biological systems.

For instance, new light has been shed on how the suprachiasmatic nucleus (SCN) in the hypothalamus is reciprocally interconnected to the thalamic intergeniculate leaflet and prectectal olivary nuclei (PON) to keep our bodies in tune with external cues. In the brain, molecular clocks link to the outside world through eye photoreceptors, whose signals may have major influence on mental and metabolic diseases.[4,5] Sunlight processed by the retina activates circadian gene expression in the SCN through a series of signal-transduction events by melanopsin—expressing photosensitive retinal ganglion cells. It is unclear how melanopsin signaling drives non-image and image-forming pathways,[4,6] or how cones and color influence mammalian circadian photoentrainment.[7] However, retinal output directed at three mutually interrelated retino-recipient nuclei in the brain appears to be under direct control of a local circadian oscillator dependent on neuropsin-expressing (Opn5) ganglion cells and indirectly influenced by the PON, which controls pupil aperture.[7] A temporal gating mechanism seems to maximize circadian sensitivity to light at dawn and dusk.[7]

Unsurprisingly, modern lifestyles often lack sufficiently strong daily circadian timing stimuli, which can have negative health impacts. PR synchronization is essential for many biological functions. For example, spontaneous and stimulus-induced neuronal rhythmicity and resulting cell ensemble oscillations are required for central nervous system function.[8] At the pathological end of the spectrum, neurological illnesses [e.g., Parkinson's disease, Alzheimer's disease (AD), stroke, and epilepsy] are associated to abnormal cerebral oscillatory profiles. In AD, there is strong evidence that an impaired resting state cortical alpha activity correlates with cognitive deficit and disease severity. It has also been argued that ''a constant and reliable hallmark of AD across electroencephalogram (EEG) and magnetoencephalography studies is the significant decrease of coherence at alpha frequency in temporo-parietal areas.''[9] Likewise, major wave components of the electroretinogram (ERG), a study that measures the global electrical response of the retina, are severely affected in humans with glaucoma or ocular hypertension.[10] ERG oscillatory potentials (OPs), which reflex metabolic alterations and neuronal dysfunction in the retina,[11] have also been described as reduced in amplitude or delayed in complex diseases (CDs) such as diabetic retinopathy, glaucoma, vascular occlusions, and age-related macular degeneration (AMD).[12,13]

PR reestablishment is complex because PRs exhibit nonlinear dynamics that originate from the combined influence of noise inherent to biological systems as well as deterministic and non-fully deterministic mechanisms within a fluctuating chaotic environment.[14,15] At a basic level, PRs stem from electric-charge movements and exist in myriad spatio-temporal scales within tissues—themselves, energy-dependent constructs made up of biomolecules and water.[16] Yet literature suggests that external signals such as low-level energy light (as well as pulsed weak electric and magnetic fields) may be able to help reestablish altered PRs, as suggested by the fact that oscillatory states can act as carrier signals for temporal coding, and pulsating signals have transduction functions.[3,17] For instance, a series of 20 patients with AD treated using transcranial infrared brain stimulation with a 1064-nm PBM-range laser applied to the right forehead suggests improved cognitive function. EEG data showed neuromodulation of the ipsilateral, fronto-parieto-occipital network, and contralateral, parieto-occipital network at the alpha frequency during the 11-min stimulation period.[18] In addition, an AD case with significant cognitive improvement after transcranial plus intranasal PBM treatment displayed oscillation changes in the delta, theta, and alpha frequency bands of the EEG.[19]

In our own research, a case report of a patient with bilateral geographic atrophic AMD and associated neurologic disease, treated with PBM using an infrared pulsed laser device (IPLD; 904 nm, modulated to 3 MHz) noninvasively and at distance (i.e., external supplementation of the photic energy in the near infrared reaches the retina without direct application to optical tissues), showed neurologic improvement and functional and structural ocular changes.[20] The latter

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encompassed ''lower intraocular pressure (IOP) consistent with a retrospective noncomparative analysis of patients treated with the IPLD, which revealed statistically significant IOP hypotensive effects.''[20,21] ERG changes showed that the cone b-wave implicit time decreased during the photopic phase (30 Hz flicker), and the opposite occurred in the white single-flash mixed rod and cone b-wave implicit time throughout the scotopic phase. In addition, the appearance of previously unrecordable OPs, and increased photopic and scotopic a- and b-wave amplitude were displayed, suggesting a global post-IPLD treatment tendency toward a normal rhythm.[16,20] In addition to light-induced changes in the transretinal movements of ions, principally sodium and potassium, in the extracellular space that result in an improved diffuse bioelectric response of the retina, the appearance of OPs is strongly suggestive of IPLD-dependent increased retinal flow and oxygenation, which would induce better neural function. These results are in accord with *in vivo* studies using ERG as an indicator of retinal function, wherein significant recovery of photoreceptor-mediated retinal signals has been reported in light-emitting diode-treated rodents, suggesting that PBM may enhance recovery from retinal injury redox potential and other ocular diseases.[22]

We have proposed that PRs may be reactivated and synchronized through water, CO_2, and membrane receptors by selective, noninvasive, long-range, external energy supplementation. While a full elucidation of this idea exceeds this article's scope, its foundations can be partly summed as follows: as per the Stark–Einstein law, photochemical change can only be triggered by absorbed light. Water's absorption coefficient (AC) at <1100 nm is relatively low. Still, water is a biologically important photo acceptor in the 600–1100 nm range for multiple reasons.[23] First, humans are ~60–70% water by weight. In fact, water makes up ~99% of our molecules due to its small molecular weight.[24] Second, higher ACs can be reached at lower or higher intervals through harmonic/anharmonic resonance. Third, light-induced vibrations act as Hamiltonian dynamic systems, which exhibit complex nonlinear, time-dependent chaotic behavior that strongly enhances molecular interaction. Moreover, the human body can be in resonance while energy is transferred among different modes or trajectories, magnifying energy absorption and transport due to its multi-fractal architecture.[25]

Differences in oxidation–reduction (redox) potential between degrading and well-oxygenated tissues translate into significant injury potentials. This allows diseased tissues to be selectively targeted in accord with the extension of second law of thermodynamics and Onsager's theory of reciprocal relations.[26] Studies further show that water provides efficient pathways for charge storage, separation, and subsequent release.[24,25] Enhanced water structuring favors energy-dependent network protein and signaling node activity, which are generally altered in cancer and other CDs such as vascular syndromes (e.g., peripheral arterial disease) and neurodegenerative diseases of retina and brain. Pulsed signals may reactivate and modulate metabolic control levels through two complementary pathways: (1) molecular hydrophobic forces such as folding/unfolding of proteins and DNA/RNA self-assembly and (2) hydrophilic interfaces, including the exclusion zone, which has been shown to be able to separate and store charges, thus acting as a potential energy reservoir. Such charges may later fuel intracellular electron (OH^-) transfer and proton (H^+) movement in the bulk's aqueous flow for cell signaling.[24,27] Thus, light-water interactions may represent a novel pathway for the coupling of PRs by external energy transfer in a highly efficient multi-fractal regime.[23,28]

This article seeks to revisit and highlight the growing relevance of the seemingly simple, but powerful, idea that repetitive low-energy forces of certain parameters can profoundly affect human physiology in light of last year's Nobel Prize in Medicine or Physiology and other major advances. Based on the state of the art, we are convinced that light-water interactions in tissues by PBM will one day be able to selectively power and modulate PRs to help reestablish homeostasis–homeokinesis in higher biological systems. While not a panacea, this approach offers unique potential for multiple CDs. Challenges include developing and testing new treatment systems and documenting underlying mechanisms.[23]

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References

1. Hall JC, Rosbash M, Young MW. The Nobel Prize in Physiology or Medicine 2017. Available at: http://www.nobelprize.org/nobel_prizes/medicine/laureates/2017/ (Last accessed October 2, 2017).
2. Lanzafame RJ. Editorial: good vibrations: more evidence of reciprocity? Photomed Laser Surg 2007;25:465–466.
3. Santana-Blank LA, Rodríguez-Santana E. Physiologic rhythms responding to low-level electromagnetic and mechanical signals: the Joule equivalence principle. Photomed Laser Surg 2008;26:405–406.
4. Kuehn BM. Resetting the circadian clock might boost metabolic health. JAMA 2017;317:1303–1305.
5. Foster RG, Kreitzman L. The rhythms of life: what your body clock means to you! Exp Physiol 2014;99:599–606.
6. Hughes S, Jagannath A, Rodgers J, Hankins MW, Peirson SN, Foster RG. Signalling by melanopsin (OPN4) expressing photosensitive retinal ganglion cells. Eye 2016;30:247–254.
7. Brown TM. Using light to tell the time of day: sensory coding in the mammalian circadian visual network. J Exp Biol 2016;219:1779–1792.
8. Llinás RR. The intrinsic electrophysiological properties of mammalian neurons: insights into central nervous system function. Science 1988;242:1654–1664.
9. Assenza G, Capone F, di Biase L. Oscillatory activities in neurological disorders of elderly: biomarkers to target for neuromodulation. Front Aging Neurosci 2017;9:189.
10. Holopigian K, Seiple W, Mayron C, Koty R, Lorenzo M. Electrophysiological and psychophysical flicker sensitivity in patients with primary open-angle glaucoma and ocular hypertension. Invest Ophthalmol Vis Sci 1990;31:863–868.
11. Wachtmeister L. Oscillatory potentials in the retina: what do they reveal. Prog Retin Eye Res 1998;17:485–521.
12. Hancock HA, Kraft TW. Human oscillatory potentials: intensity-dependence of timing and amplitude. Doc Ophthalmol 2008;117:215–222.
13. Walter P, Widder RA, Luke C, Königsfeld P, Brunner R. Electrophysiological abnormalities in age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol 1999;237:962–968.

14. Glass L. Synchronization and rhythmic processes in physiology. Nature 2001;410:121–126.
15. Shinbrot T, Muzzio FJ. Noise to order. Nature 2001;410: 251–258.
16. Santana-Blank L, Rodríguez-Santana E, Santana-Rodríguez K. Theoretic, experimental, clinical bases of the water oscillator hypothesis in near-infrared photobiomodulation. Photomed Laser Surg 2010;28:S41–S52.
17. Hess B. Periodic patterns in biochemical reactions. Q Rev Biophys 1997;30:121–176.
18. Wang X, Dmochowski J, Husain M, Gonzalez-Lima F, Liu H. Proceedings #18. Transcranial infrared brain stimulation modulates EEG alpha power. Brain Stimulation 2017;10: e67–e69.
19. Zomorrodi R, Saltmarche AE, Loheswaran G, Ho KF, Lim L. Complementary EEG evidence for a significantly improved Alzheimer's disease case after photobiomodulation treatment. Alzheimer Dementia 2017;13(S7):P621.
20. Rodríguez-Santana E, Reyes H, Santana-Rodríguez KE, Santana-Blank L. Photo-infrared pulsed biomodulation in age-related macular degeneration associated to neurological disease: one interventional case report and minireview. J Chin Clin Med 2008;3:470–477.
21. Rodríguez-Santana E, Santana-Blank LA, Santana-Rodríguez KE. Hypotensor effect of photo-infrared pulsed biomodulation over intraocular pressure. J Chin Clin Med 2011;6:147–157.
22. Eells JT, Henry MM, Summerfelt P, et al. Therapeutic photobiomodulation for methanol-induced retinal toxicity. Proc Natl Acad Sci USA 2013;100:3439–3444.
23. Santana-Blank L, Rodríguez-Santana E, Santana-Rodríguez KE, Santana-Rodríguez JA, Reyes H. Water's many roles in laser photobiomodulation. J Cancer Res Treat 2015;3:1–5.
24. Pollack GH. The enigma of interfacial water. In: The Fourth Phase of Water: Beyond Solid, Liquid, and Vapor. GH Pollack (ed.). Seattle, WA: Ebner and Sons, 2013; pp. 25–41.
25. Santana-Blank L, Rodríguez-Santana E, Santana-Rodríguez JA, Santana-Rodríguez KE, Reyes H. Water as a photoacceptor, energy transducer and rechargeable electrolytic biobattery in photobiomodulation. In: Handbook of Low Level Laser (Light) Therapy. M Hamblin, T Agrawal, M de Sousa (eds.). Singapore: Pan Stanford Publishing, 2016; pp.119–134.
26. Rubi JM. The long arm of the second law. Sci Am 2008; 299:62–67.
27. Hamasaki T, Harada G, Nakamichi N, et al. Electrochemically reduced water exerts superior reactive oxygen species scavenging activity in HT1080 cells than the equivalent level of hydrogen-dissolved water. PLoS One 2017;12:e0171192.
28. Hohlfeld RG, Cohen N. Self-similarity and the geometric requirements for frequency for frequency independence in antennae. Fractals 1999;7:79–84.

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