The Cellular Redox Process

Laser Therapy: Exploring the Role of Redox Mechanisms (Low-Level Light Therapy)

Introduction

CELLULAR REDOX STATE is the delicate balance between the levels of reactive oxygen species (ROS) produced during metabolism and ROS scavenged by the antioxidant system.[1] ROS are largely produced as oxidative metabolism byproducts of the mitochondria. These ROS alter the cellular redox state. In higher concentrations they can be cytotoxic; however, in lower concentrations they are now being appreciated as important signaling molecules. In certain cell types, they have demonstrated their effect on cellular function, in particular as growth regulators.[2] In plants, the chloroplast is a major source of ROS, produced by photostimulation of the chloroplast electron transport chain.

Photosynthesis is dependent upon the absorption of photon energies from the visible and near visible spectrum. Plant life utilizes biomolecular photoacceptors to absorb this energy. Subsequent photoexcitation is tightly linked to biomolecular electron transport, which in essence involves the oxidation and reduction of biomolecules in the chain. This electron transport is used to create the proton motive force and thus generates energy for the cell. This electron transport also influences the reduction and oxidation of biomolecules associated with the electron transport chain (i.e., the production of associated ROS). In this way, visible and near visible light provides the energy for the production of high-energy molecules and influences the reduction/oxidation (redox) state of the cell.

Laser research has revealed that specific wavelengths of light in the visible and near visible spectrum (at the correct dose, intensity, and pulse frequency) can induce a variety of cellular effects in some non-photosynthetic cells.[3–13] Our understanding of such effects will help determine the clinical utility of low-intensity lasers and light-emitting diodes (LEDs). Interestingly, these cellular effects appear to share some mechanisms with the specialized processes of photosynthesis.

This review surveys several lines of evidence that implicate a relationship between light, electron transport, and cellular redox signal transduction in photosynthetic and non-photosynthetic organisms, including human beings. The intention is not to provide an exhaustive review of each individual area of research, but rather to propose a novel framework for integrating these fascinating areas of research.

Mitochondrial Photostimulation

There is now substantial evidence demonstrating the specificity with which low-intensity monochromatic light interacts with certain nonphotosynthetic cells and tissues.[3–23] In these particular cases, it is evident that low-intensity lasers and LEDs induce wavelength-specific, intensity-specific, energy density–specific, and pulsed frequency–specific effects. In certain cellular and tissue states, these effects participate in coordinated processes, such as wound healing and the modulation of chronic inflammation. Given the complexity of these processes and the

specificity of the effects of low-intensity light therapy (LILT), it appears possible that laser and LED technologies may be acting on some specific aspect of endogenous physiology.

In addition, there is now a growing body of evidence that indicates that low-intensity red and near-infrared light is acting on cells through a primary photoacceptor: cytochrome C oxidase, the terminal enzyme of the mitochondrial electron transport chain.[6,14,24–39] This evidence implies cytochrome C oxidase absorption, over other possible elements of the electron transport chain. Eells's group, for example, has demonstrated that low-intensity red light (670 nm) can modulate the effects of molecules known to directly inhibit cytochrome C oxidase activity.[30,33] Furthermore, low-intensity laser researchers Karu and Kolyakov have reported similarities between the absorption spectrum of cytochrome C oxidase and the action spectra for various biological responses of HeLa cells irradiated with monochromatic light of 580–860 nm.[36] These action spectra demonstrate peak positions in the red range (between 613.5 and 623.5 nm), the far-red range (between 667.5 and 683.7 nm), and two peak positions in the infrared range (750.7–772.3 nm and 812.5–846.0 nm). Karu's work implies absorption at the two copper centers in cytochrome C oxidase, the Cu_A binuclear center and the heme A_3/Cu_B binuclear center. This research suggests that it is in fact the oxidized form of cytochrome C oxidase, and perhaps the oxidized forms of these copper centers, that is particularly sensitive to these wavelengths of low-intensity light.[15,29,35] This suggests that pro-oxidant cellular conditions, which likely promote the oxidized form of cytochrome C oxidase, may result in increased sensitivity to red and near-infrared light.

Interestingly, LILT research has shown that certain cellular and tissue states, known to be associated with pro-oxidant conditions, demonstrate an increased sensitivity to low-intensity laser and LED biostimulation. Actively proliferating cells and chronically inflamed tissues have shown an increased sensitivity to red and near-infrared (NIR) LILT.[6,13,15,22,40–43] Among the cell types investigated, HeLa cells, fibroblasts, and epithelial cells have all demonstrated sensitivity to LILT. These cells are particularly photosensitive when they are in a proliferative phase.[44–46] In each case, the proliferative phase of these cell types is associated with a pro-oxidant redox state.[2]

At the tissue level, diabetic wounds have been shown to be more sensitive to LILT than normally healing tissue.[20,22,23,47] This may in part be due to pro-oxidant conditions associated with diabetic hyperglycemia.[48,49] Pro-oxidant conditions may promote the presence of the oxidized, more photosensitive form of cytochrome C oxidase in the mitochondria of treated tissue.[35] This, in addition to other factors such as vascular compromise and poor metabolism, might help to explain the increased LILT response in poorly healing diabetic wounds as compared to normally healing tissue.

A similar argument could be made for the increased sensitivity of chronically inflamed joints, as in the case of temporomandibular disorders. This pathology has been shown to be associated with pro-oxidant conditions and has been shown to be particularly sensitive to LILT.[42,50]

The leading theory attempting to explain the basic mechanism of LILT implicates cytochrome C oxidase as the primary photoacceptor. Once cytochrome C oxidase is stimulated by light, electron transport is accelerated, leading to increased ATP production.[26,27,51] At the same time, this photobiostimulation is linked to the generation of ROS.[11,29] This increased metabolism and transient increase in ROS then participate to provide energy and intracellular signal transduction.

The complete signal transduction pathway has not yet been clearly elucidated. However, in some cases, LILT research demonstrates that it may involve downstream modulation of intracellular pH and calcium concentrations.[8,19] Thus, photostimulation of cytochrome C oxidase is thought to lead to increased energy availability and signal transduction. This culminates in biochemical and cellular changes that lead to macroscopic effects, such as increased human epithelial cell proliferation or accelerated healing in diabetic wounds.[44,47] As mentioned above, these effects are known to be dependent upon cell type, cellular growth phase, and associated redox conditions.

The apparent photosensitivity of the mitochondrial electron transport apparatus is a relatively new addition to biological science. Leading low-intensity laser researcher Tiina Karu commented that photosensitivity might be a common property of higher animals and could have physiological significance under certain conditions, under exposure to orange-red light and in high-ADP conditions.[35] One suggestion is that exposure to orange-red light at dawn may somehow help organisms prepare their cells for exposure to higher levels of UV light in the day.

The mitochondrial electron transport chain no doubt shares an evolutionary relationship with the photosynthetic electron transport chain. Electron transport systems are fundamental to life on earth. There is a clear functional similarity between the analogous mitochondrial and photosynthetic systems. It appears possible that these biomolecular electron transport systems in certain cell types may share properties that render them sensitive to some forms of visible and near visible light.

Reactive Oxygen Species and the Electron Transport Chain

The photosynthetic electron transport chain (PETC) is the principal place of appearance of ROS in plants under illumination. It is well established that these ROS participate in cellular signal transduction in plants. "The photosynthetic electron transport chain (PETC) has the capacities both to produce and to scavenge ROS. It is accepted now that the response of plants to any environmental factor deviating from its optimal value, as well as to wounding, includes an increased production of the ROS. The control of the ROS level is necessary both to prevent oxidative stress or, more accurately, oxidative damage of cell components, and to provide some developmental processes and the response in incompatible plant-pathogen interactions.[52]"

Similarly to the PETC, animal mitochondrial production and maintenance of intracellular ROS play a significant role in biology. The development of our distant animal relative, the ancient sea urchin *Strongylocentrotus purpuratus*, provides an interesting example. In the sea urchin embryo, asymmetrical clusters of mitochondria in the cell lead to localized generation of intracellular ROS. Investigators have determined that it is this localized, intracellular ROS generation that determines the sea urchin's initial blueprint. This localized ROS generation determines the oral/aboral axis of the developing organism.[53] In reference to the organization of the mitochondria, a related phenomenon also seems to participate in LILT. Likely due to redox changes, low-intensity helium-neon lasers have been shown to alter the organization of the mitochondrial apparatus in several cell types.[25–27]

Concerning mammalian cells, R. Burdon has written a comprehensive review of redox regulation of cell proliferation in which he remarked that there is a growing body of evidence to suggest that

ROS (superoxide and hydrogen peroxide) may play a crucial role in the mechanisms underlying proliferative responses.[2] In the review, the author reports prior studies in which low concentrations of ROS were shown to be effective in stimulating *in vitro* growth of hamster and rat fibroblasts. These effects are believed to be mediated through effects on redox-sensitive regulatory proteins, including redox-sensitive transcription factors.

More recently, G. Pal et al. have conducted very elegant research investigating the effect of the low-intensity helium-neon laser on normal human skin fibroblasts.[54] Using fiber-optic nano-probes, single cells and cell populations were irradiated. Intracellular effects were then monitored with fluorescence life-time imaging. Laser-induced cellular proliferation was observed in the irradiated human fibroblasts. The study demonstrated that this induced proliferation was associated with real-time transient increases in ROS production.

In some cases, the production of ROS by the electron transport chain leads to proliferative mechanisms. In other cases, as in plants, ROS production can trigger the induction of antioxidative scavenging mechanisms. In this way, the ROS level is controlled and homeostasis is maintained. As mentioned above, low-intensity laser/LED research shows that like the PETC, the mitochondrial electron transport chain produces ROS when illuminated with certain wavelengths (e.g., 632.8, 812, and 820 nm) of monochromatic light.[11,29,54] The generation of such ROS, in addition to increased ATP production, may be involved in stimulating restorative mechanisms. Such a process might participate in the treatment of delayed wound healing or chronic inflammation in the following manner.

Pro-oxidant conditions in cells, as those found in chronic inflammation or diabetes, may promote the oxidation of cytochrome C oxidase, resulting in increased mitochondrial photosensitivity to low-intensity monochromatic light. As mentioned above, once stimulated, the "oxidized" mitochondrial electron transport chain generates ATP and ROS. Amidst increased metabolism, these particular ROS alter cellular function. In some cases they may promote proliferation, and in others they may act to induce antioxidative mechanisms that promote redox homeostasis and improve cellular functioning. In some cases, such ROS signaling could act to alter gene expression by influencing redox-sensitive transcription factors.[55–58] In fact, LILT has been shown to alter the expression of a variety of genes. In their research, Zhang et al. used cDNA microarray analysis to investigate this phenomenon and found that red light irradiation regulated the expression of 111 genes in 10 functional categories.[46] Most of these affected genes are known to directly or indirectly play roles in the enhancement of cell proliferation and the suppression of apoptosis. Several genes related to anti-oxidation and mitochondria energy metabolism were also found to express differentially upon irradiation.

Low-Intensity Ultraviolet A Photostimulation

Let us look at one more established phenomenon of photobiology. Ultraviolet (UV) light induction of DNA repair is one of the most well studied interactions of near visible light with cells. This has been of particular interest to those working with gene therapy. In the developing field of gene therapy, one approach involves using a retroviral vector to introduce a gene to a cell. To ensure the expression of the introduced gene, scientists are searching for ways to safely induce DNA polymerases involved in facilitating the expression of the viral gene. In one particular gene therapy

case, researchers have been exploring methods for activating gene transduction to treat articular cartilage defects.[59] It was previously known that ultraviolet C light (less than 280 nm) facilitates retroviral transduction by inducing DNA repair enzymes that mediate second-strand synthesis. However, UVC light causes serious side effects, including DNA damage and significant cytotoxicity. Consequently, its utility in gene therapy is limited. However, UV light closer to the visible spectrum has shown more promise. Researchers have experimented with ultraviolet A light (320–400 nm) at lower intensities (35-mW and 100-mW lasers). Ultraviolet A is not absorbed by DNA and does not directly induce DNA mutations. At lower intensities/doses, it is not significantly cytotoxic. In their study, UVA low-intensity laser light was shown to be an effective method to induce gene transduction by activating DNA polymerases. Although the basic mechanisms of signal transduction are not clear, UVA-activated gene transduction is associated with the transient increase in intracellular reactive oxygen species. This low-intensity UV stimulation of DNA polymerases, possibly through the generation of ROS, bears an interesting similarity to red and near infrared low-intensity laser stimulation. The potential photoacceptor for UVA light has not been clearly identified, although similar mechanisms may be involved.

In addition to the more widely discussed red and infrared photostimulation, Karu reports that the action spectrum of irradiated HeLa cells also demonstrates UVA-induced activation of nucleic acid synthesis. Karu also reports on experiments that have shown that a specific wavelength of UVA light (365 nm), like red and infrared light, can lead to activation of mitochondrial oxygen consumption.[29] Cytochrome C oxidase does demonstrate some UV absorption; however, more work needs to be done to explore its potential role as a UV photoacceptor in this case.[60] As in red and infrared photostimulation, other photoacceptors may be involved. Nonetheless, this UVA-induced biostimulation provides another interesting example in which near visible light appears to be generating ROS through some biomolecular photoacceptor. Subsequently, cellular functioning (i.e., DNA polymerase activity) is altered.

Conclusion

In conclusion, low-intensity monochromatic light has been shown to cause a variety of effects on irradiated cells, depending on the state (i.e., growth phase and redox conditions) of those irradiated cells. These effects appear to be clinically relevant. LILT is now used by some practitioners to treat poorly healing wounds and chronically inflamed tissues. Monochromatic light (UVA) effects are also being investigated for their potential role in gene therapy.

In these phenomena we observe physiology previously thought to be limited to photosynthetic organisms and specialized photoresponsive cells. In the case of low-intensity red and near-infrared light stimulation of several cell types, it seems that cytochrome C oxidase may act as a primary photoacceptor. Photoexcitation of this photoacceptor in the mitochondrial electron transport chain then alters cellular function, at least in part, through increased metabolism and the generation of reactive oxygen species. As in plants, these alterations influence cellular redox state and function. Furthermore, the initial redox state of irradiated cells appears to influence their photosensitivity.

Thus, low-intensity lasers and LEDs may be acting on tissues through interactions with endogenous cellular redox systems. This may explain the specificity of LILT effects. This also may

provide a framework to explain why some cells in pro-oxidant states, such as those that are chronically inflamed, are more sensitive to LILT. In these sensitive cells, LILT would provide further ROS, which may be specific to promoting proliferation, or in some cases accelerating antioxidant mechanisms. In such a scenario, these processes would provide the energy and the direction to restore redox homeostasis and improve cell functioning. Future clinical research into LILT should include a closer look at redox state. It is likely that our understanding of LILT therapy could be advanced with *in-vitro* and *in-vivo* assessments of redox conditions.

In the words of dermatologic researcher Dr. Andrzej Slominski, "life on earth since inception has depended on a constant source of energy from the burning gases of our sun."[61] There is an ancient relationship between the visible and near visible spectrum of electromagnetic radiation and the biomolecules of life. We still have much to learn about this relationship. Research into the mechanisms of LILT may be opening another chapter in our understanding.

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