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Review

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Low-Intensity Visible and Near-Infrared Light-Induced Cell Signaling Pathways in the Skin: A Comprehensive Review

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Abstract

Objective: To describe current knowledge regarding established and putative cell signaling pathways involved in skin photobiomodulation.
Background: The skin is the largest and most accessible organ of the body. It is the first line of defense against the external environment, including solar radiation. Among solar rays, visible and infrared non-ionizing photons may reach human skin and trigger a cascade of non-thermal cell signaling pathways called photobiomodulation (PBM). The use of PBM using artificial light sources has been known for more than 50 years, but it has not yet been widely accepted due to uncertainty about the cellular mechanisms of action. However, much knowledge has been gained in this field in recent years, which will be summarized in this review.
Methods: An extensive literature review was performed using Medline, Embase, and Google Scholar as research databases to acquire relevant publications in this particular field.
Results: A comprehensive description of chromophores, primary and secondary effectors is provided in addition to a visual representation of known and putative cell signaling mechanisms involved in such complex light-skin interactions. Also, a summary of clinical indications of skin PBM, key light parameters, and promising skin applications (local and systemic) are mentioned.
Conclusions: In PBM, skin cells are the first to absorb photons, triggering specific cell-signaling pathways through primary and secondary effectors, leading to enhanced cell repair and survival, notably in hypoxic or stressed cells. A better understanding of the mechanisms of action will help us optimize known indications and discover new ones.

Keywords: photobiomodulation, low-level light therapy, phototherapy, light, skin, cytochrome C oxidase, mitochondria, ion channels, opsins, light therapy

Introduction

As for plants, the skin can absorb solar rays beyond ultraviolet radiation (UVR). Our ancestors knew that the sun could be harnessed to promote health. Romans, Greeks, Egyptians, and Babylonians all recognized that the sun had powerful curative properties. Around 400 B.C., Hippocrates promoted sunbathing and constructed a large solarium at his treatment center on the Greek island of Cos.[1] Today, we are still learning from the sun's ability to improve people's lives, notably at low intensity harmless visible and near-infrared (NIR) light wavelengths reaching the skin. Biomimicry can

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provide some clues by observing daily fluctuations in intensity and solar emission spectra.

Indeed, beneficial visible and infrared (IR) wavelengths are more prominent in the morning and late afternoon, conferring cutaneous preconditioning against harmful zenithal UVR at noon and skin repair, later in the day.[2] As a result of technological innovations like lasers and light-emitting diodes (LEDs), we can now imitate part of the solar emission spectra for therapeutic purposes. The use of low-intensity light in the visible and NIR spectra to treat humans and animals is called photobiomodulation (PBM).

Photosynthesis Versus PBM

Plant cells absorb visible light (i.e., 380–740 nm) through their chloroplasts to synthesize adenosine triphosphate (ATP), and ultimately carbohydrates,[3] a process called photosynthesis. Like plants, human cells also absorb the energy of light, and it is not only limited to UV. Recent studies have demonstrated the modulation of several cell signaling pathways following cell-absorption of visible and NIR.[4,5] Subsequently, this light-dependent modulation generally abrogates cellular imbalances caused by some physiological states, such as inflammation or hypoxia.

The skin is the largest organ of the body (with a surface of $2\,m^2$) and the first interface of living cells that is capable of absorbing light (photons) like the leaves of a tree. By natural ways, morning or late-afternoon sun rays provide these visible and IR wavelengths in higher proportion to the human body, especially skin cells.[2,6] Artificially, using low-intensity light via lasers or LEDs, this spectrum can be reproduced with more specificity and flexibility.

Light-tissue interactions are defined according to light intensity and exposure time (Fig. 1). Unlike destructive (thermal) light-based devices such as ablative lasers in photomedicine, low-intensity light therapy uses non-thermal photons. For a long time, it has been referred to as low-level laser therapy (LLLT), although it is now named PBM.[7] The term ''PBM'' is more descriptive since it implies using visible and NIR light (Fig. 2) to modulate a cellular response, thus helping cells to self-correct if necessary.

Many studies show its capacity to accelerate the healing process in acute healing disorders, like diabetic wounds.[8–12] Also, PBM can modulate acute and chronic inflammatory disorders by stabilizing cytokine signaling.[13–17] As a result, there are now many medical specialties using PBM, including dermatology, surgery, rheumatology, neurology, psychiatry, and ophthalmology (and the list is expanding).

Despite more than 50 years of research, thousands of peer-reviewed articles, and widespread use, PBM is still not mainstream medical therapy. One of the main reasons is the uncertainty about the mechanisms of action at the molecular and cellular levels.[18] This review intends to improve our understanding of the cell signaling pathways involved in the course of low-intensity light exposure, notably in the skin.

Several photon acceptors (i.e., chromophores) absorbing visible and NIR light have been identified in PBM. Well-documented chromophores and other PBM-related molecules will be discussed from a historical perspective, followed by a detailed review of the known effector molecules involved in putative cell signaling pathways.

Established Chromophores of PBM

Regardless of well-known skin chromophores like melanin, hemoglobin, and water targeted by high-energy light sources to achieve selective photothermolysis, low-intensity PBM aims at more discrete chromophores.[19]

Cytochrome C oxidase

Red and NIR light absorption largely centers around cytochrome C oxidase (CCO) as the primary chromophore in PBM, mainly unit IX of the electron transport chain located in the inner mitochondrial membrane. CCO is responsible for the final reduction of oxygen (O_2) to water using essential redox cofactors formerly generated through glycolysis and the tricarboxylic acid cycle.[20] CCO transmembrane enzyme activity may be inhibited by nitric oxide (NO), especially in hypoxic or damaged cells.

This inhibitory NO can be dissociated by photons of light (i.e., photodissociation) absorbed by CCO, containing two

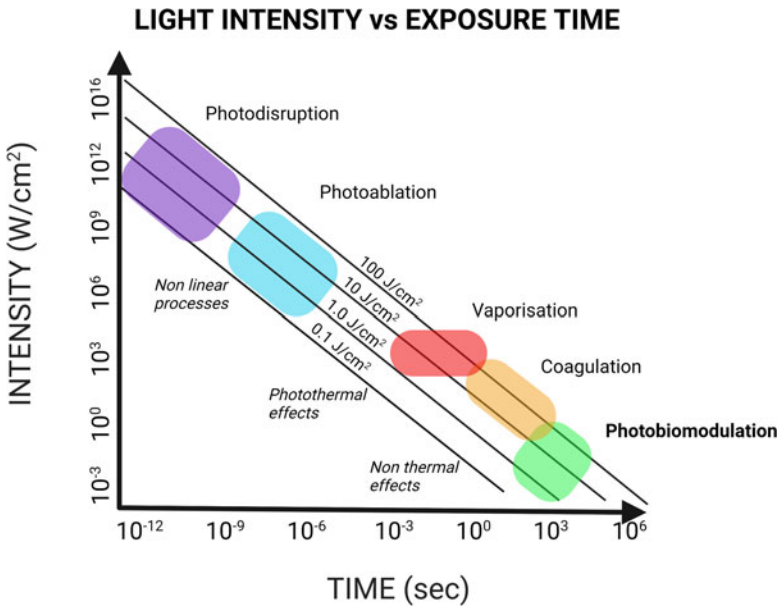

FIG. 1. Light-based device intensity versus exposure time and ensuing effects on tissues. This figure was designed on *Biorender*.