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The symbiosis of phototherapy and photoimmunology☆

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Abstract The health benefits of natural sunlight have been noted since the rise of civilization, even without the knowledge of its mechanisms of action. Currently, phototherapy remains an effective and widely used treatment for a variety of skin diseases. Ultraviolet radiation, from either the sun or artificial light sources, has a profound immunomodulatory effect that is responsible for its beneficial clinical outcomes. Ultraviolet radiation mostly induces the innate while suppressing the adaptive immune system, leading to both local and systemic effects. It is antigen specific, acts on both effector and regulatory T cells, alters antigen-presenting cell function, and induces the secretion of cytokines and soluble mediators. This review provides an overview of the immunologic mechanisms by which ultraviolet radiation is responsible for the therapeutic effects of phototherapy.

Introduction

Throughout the course of history, phototherapy has had a substantial role in the management of a wide variety of skin diseases. Even without the recognition of its mechanisms, benefits of natural sunlight were known long before the introduction of artificial light sources. In this review, we provide an overview of several mechanisms thought to be responsible for the local and systemic biologic effects of incident ultraviolet radiation (UVR) and the therapeutic effects of phototherapy.

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Electromagnetic spectrum

UVR is electromagnetic radiation with wavelengths from 100 nm to 400 nm, bordering with the highest frequencies of visible light. Its name derives from the Latin word *ultra*, meaning "beyond," because it is "beyond" violet from the visible light spectrum. UVR is then subdivided into ultraviolet C (UVC) (100-280 nm), UVB (280-315 nm), and UVA (315-400 nm). There are subtle differences in the wavelength subdivisions, which vary throughout the literature on the subject. Considering the distinct biologic effects caused by different wavelengths, UVB and UVA radiation have been further subdivided into broadband UVB (280-320 nm), narrowband UVB (311-313 nm), UVA-2 (315-340 nm), and UVA-1 (340-400 nm) (Figure 1).

The ozone layer, together with atmospheric oxygen, block most solar radiation before it reaches the earth; it blocks virtually all UVC, and approximately only 5% of remaining

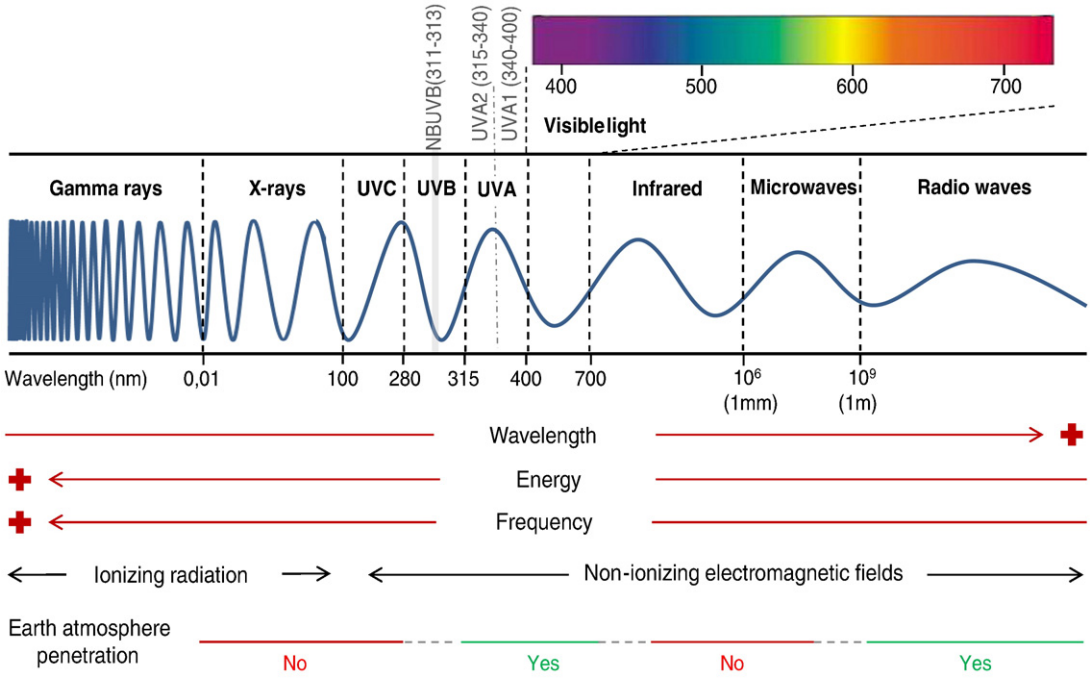

Fig. 1 Electromagnetic spectrum. UVA, ultraviolet A; UVB, ultraviolet B.

ultraviolet (UV) of longer wavelengths reaches the earth (96.65% UVA and 3.35% UVB).[1] Terrestrial radiation varies with the path that solar radiation takes to transverse through the ozone layer, air pollution, and solar altitude, which then depends on geographic location, season, and time of day. UVA radiation is constant throughout the day, and approximately half of its exposure occurs while in the shade as a consequence of surface reflection and cover (eg, clouds and windows) penetration, whereas UVB peaks around noon and mostly requires direct exposure (Figure 2).[2]

UVR and the skin

Once the light hits the skin, it can be reflected, scattered, or absorbed. Although scattering occurs mostly in the dermis due to collagen, UVB (having a shorter wavelength) is predominantly absorbed in the epidermis and upper portion of the dermis. Longer-wavelength UVA penetrates well into the dermis.[3] Absorption of the radiation by chromophores leads to photochemical reactions and potential immunoreactions. Chromophores are molecular components capable of absorbing wavelengths. Each chromophore can only absorb a certain range of wavelengths, denoted as its absorption spectrum, and the absorption maximum is the wavelength(s) with highest probability of being absorbed.[4] Chromophores include DNA, nucleotides, lipids, amino acids, porphyrins, photosensitizing drugs, and tattoo pigments, among others (Figure 3).

Immune modulation of phototherapy

Although UVR exposure induces mostly local immunosuppression in the skin, it can also lead to systemic modulation through cytokine secretion by irradiated epidermal cells.[5] UVR properties can also be classified according to their direct, indirect, immediate, delayed, acute, or chronic effects. Unfortunately, phototherapy produces mostly immediate and temporary effects, requiring multiple and consecutive sessions to be efficient.

The anti-inflammatory action of phototherapy occurs through multiple photobiologic pathways activated based on exposure to specific types of UVR. UVB has been mostly used to treat psoriasis, cutaneous T-cell lymphoma, and atopic dermatitis. Because it only penetrates into the superficial portion of the dermis, it results in the reduction of epidermal Langerhans cells, while inducing keratinocytes to secrete immunosuppressive cytokines and change T-cell adhesion molecules. In the stratum corneum, it converts *trans*-urocanic acid to *cis*-urocanic acid; however, UVB has a primary and direct effect on DNA, generating cyclobutane pyrimidine dimers, which can be mutagenic and inhibit polymerases, leading to replication arrest.[6]

UVA1 has also been found to be effective in treating cutaneous T-cell lymphoma by directly causing the apoptosis of $CD4^+$ T cells.[7] Its efficacy in mastocystosis is caused by depletion of mast cells from the skin.[8] In morpheaform and sclerodermoid conditions, it upregulates expression of matrix