Photodynamic Therapy

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KEYWORDS

• Photodynamic therapy • Aminolevulinic acid • Methyl aminolevulinate • Nonmelanoma skin cancer • Light-based therapies

KEY POINTS

- Over the past 100 years, photodynamic therapy (PDT) has evolved into a safe and effective treatment option for actinic keratosis, superficial nonmelanoma skin cancer (NMSC), and more recently, photoaging, acne, and verrucae.
- PDT is the interaction among 3 ingredients: light, a photosensitizer, and oxygen. This interaction generates reactive oxygen species (ROS), especially singlet oxygen radicals, which cause cell death by necrosis or apoptosis.
- The 2 commonly used photosensitizers, aminolevulinic acid (ALA) and methyl aminolevulinate (MAL), are metabolized by cells into the photoactive porphyrin, protoporphyrin IX (PpIX). Thus, an incubation period is required.
- Red or blue light are commonly used light sources to activate the photosensitizer.

INTRODUCTION

PDT relies on the interaction between a photosensitizer, the appropriate wavelength, and oxygen. The reaction generates ROS in cells that take up the photosensitizer, causing cell death by necrosis or apoptosis, but spares the surrounding tissue. Initially, PDT relied on systemic administration of the photosensitizer, but the advent of a topical application revolutionized the field. Over the past 100 years, PDT has evolved into a safe and effective dermatologic treatment option for actinic keratosis/cheilitis, superficial NMSC, and more recently, photoaging, acne, sebaceous hyperplasia, and verrucae.[1,2] Furthermore, PDT has also expanded outside dermatology, and it is now used as adjuvant therapy to treat pulmonary, respiratory tract, neural, and urinary tract tumors, as well as vitreoretinal disease.

HISTORICAL PERSPECTIVE

Ancient civilizations have known for thousands of years that they could combine different plants with sunlight to treat various skin diseases. It was not until about 100 years ago that Hermann von Tappeiner[3] coined the term photodynamic action to describe an oxygen-dependent reaction after photosensitization. He noted that in the absence of oxygen, dye and light alone did not cause cell death. He continued to develop the concept of PDT, and eventually described the first cases in humans, using eosin as the photosensitizer to treat various skin conditions, including condyloma lata and NMSC.

Over the years, many photosensitizers have been used, and the most studied agent is hematoporphyrin. However, hematoporphyrin had to be administered intravenously and was cleared from tissue slowly, resulting in prolonged phototoxicity. It was not until 1990 that Kennedy and colleagues[4] reported the use of 5-ALA and visible light for topical PDT treatment of the skin. ALA was revolutionary, because it easily penetrated damaged or abnormal stratum corneum and rapidly cleared. Using a single application to treat basal cell carcinoma (BCC), Kennedy and colleagues[4] were able to achieve a 90% complete response rate.

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MECHANISM OF ACTION

PDT is the interaction among 3 ingredients: light, a photosensitizer, and oxygen (**Fig. 1**). After exposure of the photosensitizer to light containing its action spectrum, ROS, especially singlet oxygen radicals, are generated. The ROS affect all intracellular components, including proteins and DNA, resulting in necrosis or apoptosis.[2] Thus, only cells with intracellular photosensitizer are selectively damaged, and the surrounding tissue is spared, resulting in an outstanding cosmetic result.

SENSITIZER

The multiple early photosensitizers, including eosin red and the hematoporphyrin derivatives, were not widely used in dermatology because they had an unfavorable side effect profile.[3] The advent of 5-ALA revolutionized PDT. The photosensitizer 5-ALA has a low molecular weight, which allows it to easily penetrate the stratum corneum and be cleared from the skin within 24 to 48 hours of application.[2] ALA is the first compound synthesized in the porphyrin-heme pathway (see **Fig. 1**) and is converted endogenously into the photosensitizer PpIX. Once PpIX is exposed to its action spectra (including 400–410 nm and 635 nm), ROS are generated, which destroy the target cell. Although the heme synthesis pathway is controlled by ALA synthase, exogenous ALA bypasses this rate-limiting enzyme and overwhelms the cell's ability to convert PpIX into heme. ALA is thought to preferentially target tumors of epithelial origin because of their defective epidermal barrier and slower conversion of PpIX into heme. In the United States, ALA is available as a 20% solution and is marketed under the trade name Levulan.

An alternative to ALA is the methyl ester form, MAL.[2] The presence of methyl ester group makes the molecule more lipophilic and enhances penetration; however, it must be converted back to ALA by intracellular enzymes. Although this may limit the availability of ALA, MAL has been shown to have better tumor selectivity and to reach maximal intracellular concentrations of PpIX quickly, allowing a shorter incubation period. In the United States, MAL was available for a brief period as a 16.8% cream under the trade name Metvixia. However, it is currently unavailable in the US market because of economic reasons, but remains widely used in Europe.

LIGHT SOURCE

Several light sources, including coherent and incoherent light, have been used in PDT. PpIX has a strong absorption peak at 405 nm, along with

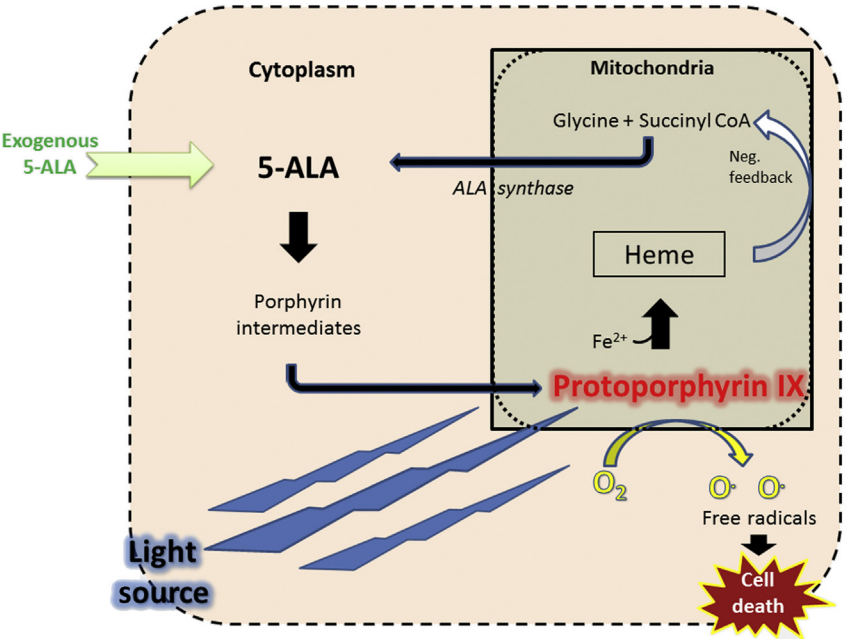

Fig. 1. Mechanism of photodynamic therapy. Exogenous ALA enters the porphyrin-heme pathway and is converted endogenously into the photosensitizer PpIX. Once PpIX is activated by the proper wavelength of light, it produces singlet oxygen free radicals, which destroy the target cell.