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TRP Channels as Molecular Transducers of Cutaneous Photosensitivity: Mechanisms and Clinical Implications

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Abstract Cutaneous photosensitivity is one of the most common skin reactions linked to both systemic and topical drug use, and it can manifest in the form of phototoxicity and/or photoallergy. Both reactions are triggered by the exposure of a photosensitive drug to UV radiation, but they differ in the time interval until the onset of symptoms, whether they are dose-dependent, and to what extent the immune system becomes involved. At molecular level, these photosensitive drugs absorb UV energy and then release it through reactions that generate harmful byproducts including reactive oxygen species, damaging skin cells. Less understood is how these photochemical events are translated into clinical manifestations, such as pain, redness, and inflammation. A main role in this translation seems to be attributed to Transient Receptor Potential (TRP) channels, especially TRPA1 and TRPV1 which are known to be activated or modulated by light and are also sensitive to reactive molecules produced during drug photoreactions. Alongside TRP channels, a family of non-visual opsins, originally identified in the eye but now found in keratinocytes, melanocytes, and fibroblasts, appear to function as a separate, parallel light-sensing system in the skin. Together, these two systems may explain how UV-activated drugs and their byproducts give rise to the clinical symptoms of photosensitivity, potentially through a neuroendocrine-like signalling route where skin cells send signals post-UV exposure to nearby nerve endings. However, most current research treats TRP channels and opsins as separate entities, leaving the connection between these two pathways unclear.

Keywords: TRP, photosensitivity, opsins, pain, photoallergy

Introduction

Photosensitivity is one of the most prevalent skin-related side effect of either systemic or topical drug administration (Kommu et al., 2026). Cutaneous photosensitivity comprises a multitude of sun-induced adverse drug reactions, with photoallergy and phototoxicity being the most characterized (Kowalska et al., 2021). Beyond drug-induced forms, photosensitivity is also associated with hereditary photosensitivity disorders - such as porphyrias and xeroderma pigmentosum - as well as autoimmune photodermatoses, including polymorphous light eruption and cutaneous lupus erythematosus (Lecha et al., 2009; Kuhn et al., 2014; Babes et al., 2016), all of which share the common clinical hallmark of an exaggerated cutaneous response to physiologically harmless light exposure.

Clinically, cutaneous photosensitivity presents as a spectrum ranging from mild erythema to severe burning pain, and represents the principal dose-limiting adverse effect of photodynamic therapy (PDT) as well as the defining symptom of erythropoietic protoporphyria (Lecha et al., 2009; Warren et al., 2009).

At the molecular level, photosensitivity is initiated by photosensitizer excitation, which generates reactive oxygen species (ROS) - particularly singlet oxygen and superoxide anion - via Type I and Type II photoreactions (Cosa 2004). These reactive intermediates modulate the activity of ion channels expressed in cutaneous sensory nerve endings and keratinocytes, among which the Transient Receptor Potential (TRP) channels have emerged as central molecular mediators coupling light exposure to neuroinflammatory and nociceptive responses (Trevisani et al., 2007; Camponogara et al., 2020; Woo et al., 2021; Camponogara and Oliveira 2022; Xiao et al., 2023; Lapajne et al., 2025).

This review examines the role of TRP channels - particularly TRPA1, TRPV1, and TRPV4 - in cutaneous photosensitivity, discussing the three dominant mechanisms of light-induced activation and their implications for therapeutic development.

1. Photosensitivity

Photosensitive drugs are compounds that can absorb ultraviolet radiation, reaching a high-energy state, known as the excited state. The return to the stable state requires the molecule to dissipate excess energy, which can happen via two pathways: photophysical or photochemical. Through photophysical dissipation, the molecule will release its energy as light (fluorescence or phosphorescence) or heat, while photochemical dissipation involves the molecule reacting with surrounding biological targets, generating reactive intermediates capable of producing cellular damage. The first type of photoreaction (Type I) involves a charge transfer or hydrogen transfer between the excited sensitizer and the adjacent biological substrates, generating reactive radical species such as superoxide anions and hydroxyl radicals. Type II photoreactions involve the interaction of the excited molecule with molecular oxygen, either by electron transfer, producing reactive oxygen species, or by energy transfer, forming a singlet oxygen (Cosa 2004). The pathway an excited molecule takes to disperse the excess energy depends on its structure, with some molecules such as tetracycline being able to undergo both photophysical and photochemical pathways simultaneously (Chen et al., 2008).

Even though only 6,8% of total solar emission falls within UV radiation, this small spectrum is responsible for the vast majority of drug-induced photosensitivity reactions. Both topical and systemic xenobiotics can be exposed to UV radiation: topical treatments interact directly with the skin surface, while systemically administered drugs can reach the dermis through the bloodstream, where UV radiation can reach them (Cosa 2004).

Since UVC (180-280 nm) does not permeate the ozone layer, the UV radiation incident on the skin surface is comprised of 5% UVB (280-320 nm) and 95% UVA (320-380 nm). UVB has a higher energy, which translates to shorter wavelength, making it more susceptible to scattering and interacting with the surfaces it encounters. Therefore, UVB is largely attenuated within the epidermis, and does not penetrate further layers. Even though UVA carries less energy than UVB, the longer wavelength allows it to pass through the epidermis and reach the more profound dermis layers. These properties also reflect the symptoms of extensive UV exposure. Although UVB does not penetrate beyond the superficial dermis, its radiation carries higher energy and causes direct DNA damage and the production of reactive oxygen species, making it the main cause for sunburn and skin cancer (Nishigori et al., 2020). Despite carrying less energy, UVA radiation permeates deeper into the skin, and usually causes indirect DNA damage, through the generation of reactive oxygen species, which can degrade collagen and elastin, often being the cause of premature aging of the skin (Kobaisi et al., 2021).

1.1. Photoallergy

In photoallergic reactions, the administered drug absorbs UV light and reaches a high-energy state, leading to the formation of a new photoactivated molecule, which functions as a hapten (Andreu et al., 2010). By nature, a hapten is a small molecule incapable of eliciting an immune response independently (Mihalcik et al., 2018). This structure is also called a photoallergen, as it can bind covalently to surrounding proteins forming immunogenic photoallergen-protein complexes (Andreu et al., 2010). These complexes can then act as antigens for Langerhans cells (dendritic antigen-presenting cells of the epidermis) and can trigger a humoral and cellular immune response. Maturated Langerhans cells will migrate to the nearest lymph node, where they present the processed photoallergen to native T lymphocytes, triggering expansion and differentiation intro memory T cells that will migrate back to the skin and contribute to an inflammatory response upon re-exposure to the photoallergen (Kowalska et al., 2021). Unlike phototoxic reactions, which are localized and do not involve the immune system, photoallergic reactions are defined by their immunological basis, triggering a systemic immune response that extends beyond the site of direct sun exposure, which accounts for their broader clinical implications. Since sensitization must precede elicitation, symptoms do not occur during the first exposure to the drug, but emerge after a latency period or upon subsequent re-exposure. Moreover, photoallergic reactions are not dose-dependent like the phototoxic ones, meaning that even a small concentration of the drug can trigger an immune response in an already sensitized individual (Mihalcik et al., 2018).

Differentiating photoallergic reactions from phototoxic reactions can be challenging, as both require the same triggering conditions: the presence of a drug and UV radiation. Phototoxicity usually develops within hours of sun exposure after drug administration, whereas photoallergies follow a delayed course of several days (Kowalska et al., 2021). If there is prolonged sun exposure, these two reactions may overlap temporarily, complicating the clinical diagnosis and treatment. Moreover, photoallergic reactions can spread beyond the UV-exposed areas, especially if the drug is systemically administered (Mihalcik et al., 2018).

1.2. Phototoxicity

Regarding phototoxicity, upon sun exposure, the drug generates reactive oxygen species, free radicals and oxygen singlet or triplets, which cause direct cellular damage, especially in the areas where the drug accumulates (Monteiro et al., 2016). A more hydrophilic compound will most likely create reactive oxygen species and other free radicals, while one that is lipophilic will oxidize and denature lipidic structures (González and González 1996). In phototoxic reactions, the symptoms usually occur a few hours after sun exposure and are dose dependent, meaning that the symptoms will disappear

gradually, as the drug is excreted from the body (Kowalska et al., 2021). Unfortunately, this also implies that over-dosing or accumulation of the compound in the skin will lead to more severe symptoms. Higher concentrations of phototoxic drugs in the skin can be observed with molecules that bind to melanin, such as ciprofloxacin (Beberok et al., 2011) or paracetamol (Buszman et al., 2009). Exposure to UV light triggers the production of melanin in melanocytes, promoting melanin-binding drug accumulation. Therefore, as the body tries to protect itself from sun damage, it inadvertently creates the perfect environment for phototoxic reactions to take place in the skin (Kowalska et al., 2021). Phototoxic reactions occur exclusively at sites of UV exposure, as the damage is confined solely to areas where direct contact with radiation has taken place (Cosa 2004).

TRP channels act as photosensors: Mechanism of activation

While the photochemical mechanisms described above account for the generation of reactive intermediates and oxidative cellular damage, they do not fully explain how these events can be transduced into clinical manifestations of photosensitivity, such as pain, erythema, pruritus and neurogenic inflammation (Kowalska et al., 2021). The conversion of photochemical signals into nociceptive and inflammatory responses requires specific receptors capable of detecting reactive intermediates and translating them into cellular activation signals.

In this context, it was discovered that certain members of the Transient Receptor Potential (TRP) superfamily act as mediators of UV-induced photosensitivity. The TRP superfamily encompasses 28 different mammalian channel proteins organized into 7 subfamilies: TRPA (ankyrin), TRPC (canonical), TRPM (melastatin), TRPML (mucolipin), TRPP (polycystin), TRPV (vanilloid), TRPN (NO-mechano-potential, NOMP) (Zhang et al., 2023).

These multimodal channels act as sensors for various cellular signals, being permeable for cations such as Ca^{2+} Na^{+}, K^{+} and mediate temperature, pain and tissular stress responses. Functional TRP channels are tetramers, with each subunit containing 6 transmembrane helices, and a loop associated with the pore between the 5^{th} and 6^{th} helices. The N-terminus and C-terminus are located in the cytoplasm and vary considerably between subfamilies, conferring each channel their own functional specificity (Zhang et al., 2023).

Regarding photosensitivity, out of the 7 subfamilies, only a small number of members from the vanilloid and ankyrin group are directly relevant. Structurally, TRPA1 contains a large array of ankyrin repeat domains in the N-terminal part, which are formed of numerous reactive cysteine and lysine residues. This feature represents the molecular basis for the channel's function as a multimodal electrophile sensor, as well as displaying photosensitive properties (Andreu et al., 2010; Babes et al., 2016). In addition, TRPV1, TRPV3 and TRPV4 share the same vanilloid architecture, which confers them thermosensitive thresholds from 27-43°C, each being involved in cutaneous or corneal UV radiation responses (Zhang et al., 2023).

The transduction of light into TRP channel activation can occur through 3 distinct pathways: direct intrinsic photoactivation, indirect activation through reactive intermediates and physiological opsin-coupled phototransduction. These three pathways differ in their dependence on chromophores, their physiological or pathological role, and their kinetics, yet they ultimately converge on the same outcome. Regardless of the activation mechanism, the result is TRP channel opening, leading to Ca^{2+}/Na^{+} influx and subsequent depolarization of the host cell (Lee et al., 2009; Montell 2012; Bellono et al., 2014; Yoo et al., 2020).

The direct intrinsic photoactivation pathway involves direct photon absorption by the channel protein itself, or by an endogenous chromophore (Hill and Schaefer 2009). Consequently, this is enough to induce a conformational change to the open state in the absence of any other intermediate factor or photosensitizer. It has been demonstrated that the exposure to blue light (405 nm) of TRPA1 and to a lesser extent TRPV1, can evoke channel activation with no other pretreatment being used for photosensitizing the channels (Babes et al., 2016). This type of activation has a smaller magnitude compared to a pathological photosensitized state, but it establishes a baseline responsiveness for both TRPA1 and TRPV1, that can be further amplified by endogenous or exogenous photosensitizers.

The indirect pathway via reactive intermediates remains the dominant pathological photosensitive activation, a direct result of Type I and II photoreactions (Section 1). Singlet oxygen, superoxide anion and lipid peroxidation products such as 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA), can interact with specific cysteine residues in the N-terminal domain of TRPA1, inducing conformational changes that will further increase the channel's activity (Macpherson et al., 2007; Trevisani et al., 2007; Andersson et al., 2008). This mechanism depends solely on the electrophilicity of the reactive species and their accessibility to the protein, rather than on a specific binding pocket, explaining the diverse responsiveness of TRPA1 to chemical photoproducts. Moreover, it has been shown that pre-exposure to a sensitizer can potentiate the channel's light response, often converting baseline photosensitivity into pathological activation (Hill and Schaefer 2009; Kokel et al., 2013; Babes et al., 2016). This has been confirmed for protoporphyrin IX in porphyria (Babes et al., 2016), for 7-dehydrocholesterol in Smith-Lemli-Opitz syndrome (Xu et al., 2011; Babes et al., 2017), and for 8-methoxypsoralen in PUVA therapy (Stern 2007; Babes et al., 2021).

Lastly, physiological opsin-coupled phototransduction, represents a sensory mechanism rather than a response to a photochemical injury. It has been shown that *in vitro* exposure to physiological doses of UVA radiation of human epidermal melanocytes, leads to a retinal-dependent membrane current mediated by TRPA1, via G protein – Phospholipase C (PLC) signalling. This current is required for the UVR-induced increase in melanin synthesis (Bellono et al., 2013). A follow-up study has shown that this pathway is meditated by Gαq/11 and involves IP3-dependent calcium release from intracellular stores acting together with phosphatidylinositol 4,5-bisphosphate (PIP_2)-dependent regulation of TRPA1 (Bellono et al., 2014).

Individual TRP channels in photosensitivity

TRPA1 is one of the main transducers of cutaneous photosensitivity, as it can be modulated by all the pathways previously described (Fig. 1). In melanocytes, TRPA1 mediates UVA phototransduction that drives early melanogenesis (Bellono et al., 2013). Building on this, Bellono et al., (2014) elucidated the full molecular pathway for UV detection in human epidermal melanocytes: UV light activates a plasma membrane GPCR in a retinal-dependent manner, which leads to the activation of G protein alpha subunit q/11 (Gαq/11) and phospholipase Cβ (PLCβ), followed by the hydrolysis of PIP_2 into diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP_3). The immediate Ca^{2+} influx in the cell is caused by IP_3 activation, and is followed by a delayed and more sustained influx of extracellular Ca^{2+} ions via TRPA1 activation by PIP_2 (Bellono et al., 2014).

Moreover, TRPA1 exhibits photosensitivity to blue-light (Babes et al., 2016), and acts as the principal molecular sensor for reactive intermediates generated by UV radiation, via certain critical cysteine residues from its N-terminal ankyrin repeat domain (Macpherson et al., 2007; Andreu et al., 2010; Babes et al., 2016).

Its sensitivity to various molecular products of UV radiation has been thoroughly described in the context of hereditary photosensitivity disorders. For example, in a study investigating protoporphyria, healthy volunteers were injected with aminolevulinic acid or protoporphyrin IX to simulate the clinical manifestation of protoporphyria, which resulted in erythema and pain. Exposure of the skin to UVR will generate reactive oxygen species, in this way increasing the light sensitivity of TRPA1 (Babes et al., 2016).

Beyond hereditary photosensitivity, TRPA1 has been showed to be involved in the acute inflammatory response to UVB radiation. Fialho et al., (2020) demonstrated in a UVB-induced sunburn mouse model that topical application of the selective TRPA1 antagonist HC-030031 significantly attenuated mechanical and cold allodynia, paw edema, and myeloperoxidase activity, while reversing UVB-induced Ca^{2+} influx in spinal cord synaptosomes. UVB irradiation was shown to increase local H_2O_2 levels (a well-characterized TRPA1 agonist (Sawada et al., 2008), providing a direct causal link between UVB exposure, ROS generation, and TRPA1 activation, and positioning topical TRPA1 antagonists as a promising therapeutic strategy for sunburn-associated pain and inflammation (Fialho et al., 2020).

In the context of photosensitivity, TRPV1's predominant function is being a co-effector alongside TRPA1, amplifying TRPA1-mediated signals in cutaneous light-induced pain. This channel also plays an important role in chronic UV-induced skin damage via photoaging. Briefly, UV radiation leads to the upregulation of TRPV1 mRNA and protein expression in keratinocytes, and also to the activation of the channel, driving a Ca^{2+} influx that engages multiple downstream signalling cascades converging on matrix metalloproteinase 1 (MMP-1) - the main enzyme responsible for collagen degradation in photoaged skin. (Xiao et al., 2023). A similar mechanism operates in thermal skin aging: heat shock generated by infrared radiation induces TRPV1-mediated Ca^{2+} influx and PKC activation, driving MMP-1 expression in keratinocytes, an effect that is abolished by selective TRPV1 antagonists or TRPV1 knockdown (Li et al., 2007). In addition, increased TRPV1 mRNA levels have been also documented in human skin undergoing both natural aging and UV-induced photoaging (Lee et al., 2009). Notably, this pathway extends to the visible spectrum as well, as blue light irradiation activates and upregulates TRPV1 in keratinocytes, triggering Ca^{2+} influx and increasing the accumulation of reactive oxygen species (ROS) and the pro-inflammatory cytokine tumor necrosis factor-α (TNF-α), effects that are reversed by TRPV1 knockdown (Yoo et al., 2020). The therapeutic relevance of these findings is illustrated by nootkatol, a chemical derivative of valencene, a sesquiterpene found in the peel of Valencia oranges and other citrus fruits. This compound is capable of simultaneously blocking TRPV1 and ORAI1. Using whole-cell patch-clamp recordings, it was shown that nootkatol significantly reduced TRPV1 and ORAI1 currents. Functionally, nootkatol suppressed UV-induced melanin synthesis in melanoma cells and UV-induced MMP-1 production in keratinocytes, reflecting the distinct downstream roles of ORAI1 in melanogenesis and TRPV1 in collagen degradation, making this dual channel inhibition a viable photoaging prevention strategy (Woo et al., 2021).

The involvement of TRPV3 in UVR detection was recently demonstrated. UVB radiation has been shown to upregulate *TRPV3* gene and protein expression in keratinocytes, accompanied by increases in pro-inflammatory cytokines such as TNF-α and IL-6. Genetic ablation of TRPV3 attenuated UVB-induced ear swelling and skin inflammation in murine models, whereas topical treatments with selective TRPV3 inhibitors produced dose-dependent reductions in inflammation and lesion severity (Qu et al., 2023).

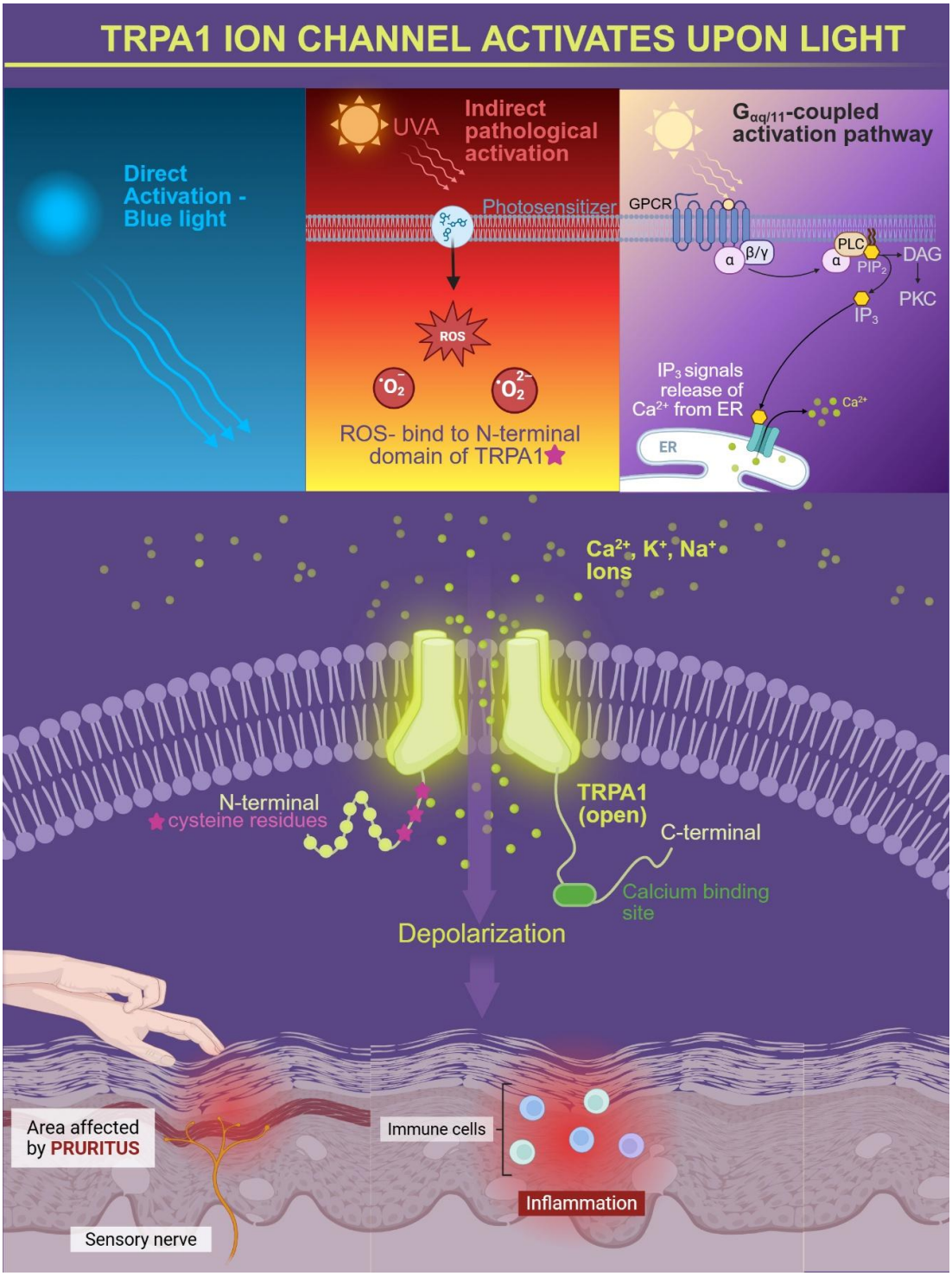

Fig. 1 Top panel: activation pathways. (1) Direct blue light activation (~405 nm) gates TRPA1 intrinsically. (2) Indirect pathological activation: UVA excites membrane-embedded photosensitizers (e.g. protoporphyrin IX in porphyria), generating ROS ($^1O_2$, $O_2•^-$) that oxidize N-terminal cysteines and promote channel opening. (3) Gαq/11-coupled GPCR pathway: UV-activated opsins engage PLC, hydrolysing PIP_2 into DAG and IP_3; IP_3 releases Ca^{2+} from the ER, DAG activates PKC, both converging on TRPA1.**Middle panel**: channel gating. Cysteine residues (pink stars) in the N-terminal ankyrin domain are the main oxidative modification site; the C-terminal Ca^{2+}-binding site modulates activity. Channel opening drives $Ca^{2+}/Na^+/K^+$ influx and membrane depolarization. **Bottom panel**: pathophysiology. In cutaneous sensory endings, TRPA1 activation triggers pruritus, burning pain, and neurogenic inflammation with immune cell recruitment — mechanisms underlying erythropoietic protoporphyria, PUVA therapy, and photodynamic therapy. **Abbreviations:** GPCR, G protein-coupled receptor; ROS, reactive oxygen species; $^1O_2$, singlet oxygen; $O_2•^-$, superoxide anion; Gαq/11, G protein alpha subunit q/11; PLC, phospholipase C; PIP_2, phosphatidylinositol 4,5-bisphosphate; DAG, diacylglycerol; IP_3, inositol 1,4,5-trisphosphate; PKC, protein kinase C; ER, endoplasmic reticulum. No AI models were used to generate this figure; Created in BioRender. Dobrin, A. (2026) https://BioRender.com/9wlajzl

Emerging evidence points to TRPV4 as a critical mediator of UV phototransduction in the corneal epithelium, adding an ocular dimension to the TRP-mediated photosensitivity landscape. Studies using primary cultures of dissociated mouse corneal epithelial cells (CECs) and debrided epithelia combined with knockout mouse models have shown that UVB exposure produces intracellular Ca^{2+} transients in mouse corneal epithelial cells, and that these responses are substantially blunted when TRPV4 is genetically or pharmacologically silenced, or when the extracellular medium is deprived of Ca^{2+}. Depletion of endoplasmic reticulum Ca^{2+} stores completely abolishes the UVB-dependent response, while genetic ablation of the UV-sensitive opsin OPN5 or pharmacological blockade of phospholipase C produces a comparable suppression. The authors constructed a functional model in which OPN5 detects short-wavelength photons and engages phospholipase C, with TRPV4 contributing to the sustained Ca^{2+} influx that follows - although whether TRPV4 is activated directly by store depletion, indirectly via PLC-generated lipid metabolites, or through a combination of both remains to be established. The physiological consequence of this cascade is the epithelial secretion of a distinct inflammatory profile - interleukin-1β and interleukin-17, matrix metalloproteinases 3 and 9, and thymic stromal lymphopoietin - implicating TRPV4 as a molecular link between corneal UV exposure and the inflammatory remodelling that characterizes ocular photodamage (Lapajne et al., 2025).

Non-visual opsins as UV light detectors

While TRPA1 and TRPV1 represent the most extensively characterized molecular detectors of UV and visible light in the skin, they are not the only photosensitive proteins expressed in cutaneous tissue. Over the last decade, a family of non-visual opsins, originally characterized in the retina (Haltaufderhyde et al., 2015), has been identified in keratinocytes (Toh et al., 2016), melanocytes (Ozdeslik et al., 2019) and fibroblasts (Lan et al., 2020), where they appear to function as an independent, parallel light-sensing system (Slominski et al., 2018).

Type II opsins, expressed in eukaryotic invertebrates and vertebrates, are G protein-coupled receptors (GPCRs) and their photosensitivity is attributed to a retinaldehyde chromophore (typically 11-cis-retinal) bound within their seven-transmembrane protein core (Castrucci et al., 2023). The chromophore absorbs incoming photons and isomerizes to its all-trans configuration, inducing a conformational change in the opsin, which leads to the activation of an associated G protein, initiating downstream signalling (Terakita 2005).

In human and/or murine skin, the main opsins identified to date are: cone opsins (OPN1), rod opsin (OPN2), encephalopsin/panopsin, (OPN3), melanopsin (OPN4), neuropsin (OPN5) and peropsin (Castrucci et al., 2023).

OPN3 has been shown to negatively modulate melanin production in human epidermal melanocytes (Ozdeslik et al., 2019). Regarding OPN5, both murine and human isoforms display an absorption maximum at 380 nm, found in the UVA range, making OPN5 the first identified human opsin with peak sensitivity in the UV spectrum (Kojima et al., 2011). A 2025 paper revealed that in mouse corneal epithelium cells, UVB induced a TRPV4 dependent Ca^{2+} influx that has been diminished by OPN5 ablation and phospholipase C inhibition. The authors proposed that TRPV4 and OPN5 work together with PLC to form a rapid alert system, although the subsequent cellular processes have not been characterized (Lapajne et al., 2025). In human skin, OPN5 has been identified in melanocytes and keratinocytes (Haltaufderhyde et al., 2015), although its role is still unclear. Kojima et al., (2011) have shown that in overexpressing HEK293T cells, OPN5 (containing the 11-cis-retinal form) activates Gi-type GPCRs in a UV dependent manner, leading to the inhibition of adenylate cyclase. This cis-retinal binging form has been found in the mouse outer-ear epithelium (one of the few bodily areas in mice which are directly exposed to UV, the others being covered in fur), suggesting that it could be a potential UV sensor. However, the downstream effects of OPN5 activation in the skin are still unclear.

Peropsin may be involved in the detection of visible violet light in human keratinocytes. In NERT-1 transfected cells, Peropsin was able to induce all-trans-retinal Ca^{2+} dependent currents, which were diminished in knockout cells (Toh et al., 2016).

TRPM1 seems to be involved in modulating the retinal-dependent calcium influx in human epidermal melanocytes, implicating that this cell type could be modulated by an opsin receptor as well (Hu et al., 2017). Unfortunately, the authors did not investigate the opsin receptor involved in this process, but the ablation and pharmacological inhibition of TRPM1 led to the inhibition of the melanosome transfer from the melanocytes to the keratinocytes in the coculture.

How could these channels regulate photosensitivity?

It is still difficult to understand whether the skin can function as a proper UV detection sensor. Based on other types of receptors found in the skin (such as temperature or pressure detectors), it would be expected that UV receptors are located on sensory neuron endings innervating the skin (Goodman and Bensmaia 2020). However, none of the opsins described in this review are directly expressed in somatosensory neurons, but rather in other skin-specific cell types (such as keratinocytes and melanocytes). The proposed model for UV detection so far has been the neuroendocrine model (Slominski et al., 2012), which states that UV-sensitive skin cells act as mediators of cutaneous UV detection mechanism. To put

it simply, UV-sensitive opsins are localized in non-neuronal skin cell types (like keratinocytes or melanocytes), and the activation of these receptors by UV light leads to a cascade of biochemical events inside the cells, culminating in the release of neurohormones, such as serotonin. These neurohormones can diffuse to nearby sensory or autonomic nerve endings, leading to systemic neuroendocrine signalling (Slominski et al., 2012).

In keratinocytes, phototoxic drugs and their photoproducts could directly activate TRP channels: reactive carbonyls and ROS generated by drugs such as fluoroquinolones or NSAIDs are structurally analogous to the 4-HNE and MDA species shown to gate TRPA1 via its cysteine-rich N-terminal domain (Babes et al., 2021). The same UV-driven Ca^{2+} influx through TRPV1/TRPV3 that mediates blue light- and UVB-induced inflammation (leading to the release of TNF-α and IL-6) could plausibly be amplified by a circulating photosensitizing drug (Fig. 2) (Kowalska et al., 2021).

In melanocytes, the cellular effects depend on melanin-binding properties of the drug: ciprofloxacin and paracetamol/ketoprofen accumulate preferentially in melanin-rich cells, placing the photosensitizer directly alongside the retinal dependent GPCR/TRPA1 cascade and the OPN3/TRPM1 modulation of melanogenesis. Here, drug-induced ROS production could plausibly perturb the same Ca^{2+} pathway that normally regulates melanin synthesis and melanosome transfer, intersecting hyperpigmentation and photosensitivity (Buszman et al., 2009).

In sensory neurons, by contrast, TRPA1/TRPV1 activation occurs due to reactive intermediates that diffuse from the epidermis (or are generated locally in proximity to the nerve terminals exposed in the dermis to systemically circulating photosensitizers), leading directly to depolarization, nociception, and neurogenic inflammation, which may account for the pain, burning, and erythema reported clinically for amiodarone and the fluoroquinolones (Kowalska et al., 2021).

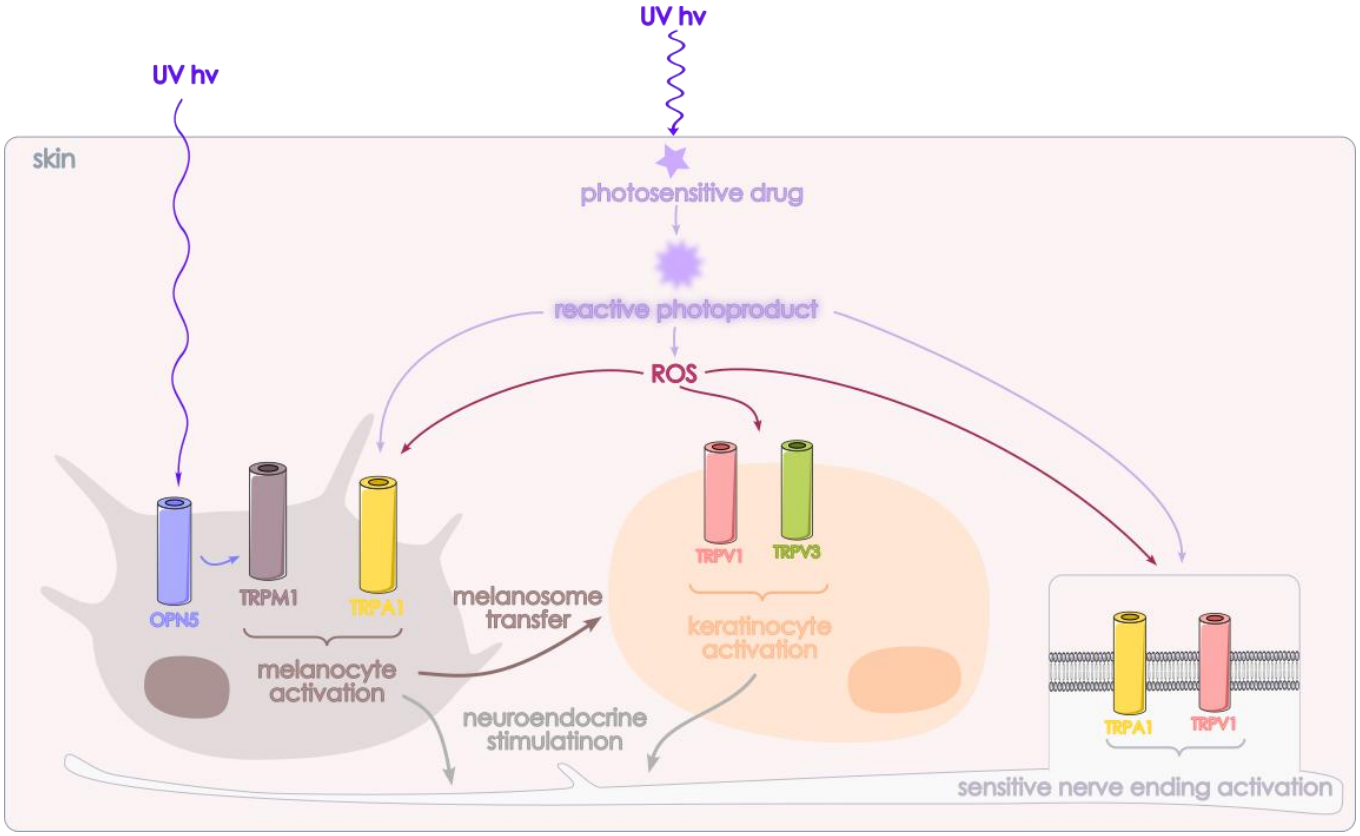

Fig. 2: Molecular mechanisms of TRP channel-mediated photosensitivity. Left (opsin-coupled pathway): UV activates OPN5 in melanocytes, engaging TRPM1 and TRPA1 to drive melanogenesis and melanosome transfer to keratinocytes. Right (ROS-mediated pathway): UV excitation of photosensitizing drugs generates reactive photoproducts and reactive oxygen species (ROS), which activate TRPV1/TRPV3 in keratinocytes (cytokine release) and TRPA1/TRPV1 in cutaneous sensory nerve endings (triggering nociception and neurogenic inflammation). No AI models were used to generate this figure; Created in Inkscape.

Conclusions

There is an abundance of evidence pointing to the involvement of TRP channels and opsins in the cutaneous photosensitizing effects of UV radiation. However, there is a lack a comprehensive understanding of how these two types of UV-sensitive receptors could interact in order to produce the clinical manifestations observed in patients. Unfortunately, most of the opsin and TRP literature is either focused on skin cellular subtypes, such as keratinocytes and melanocytes, or on the sensory innervation of the skin, with no proper bridge being formed between the two. For now, the mechanisms involved in photosensitivity are best understood as the UV-dependent activation of photosensitive opsins or TRP channels in skin cells, which would later lead to neuroendocrine signalling, or the direct activation of TRP channels by photosensitive drugs in the cutaneous somatosensory nerve endings, which would lead to pain-associated symptoms.

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