How UV Light Touches the Brain and Endocrine System Through Skin, and Why

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The skin, a self-regulating protective barrier organ, is empowered with sensory and computing capabilities to counteract the environmental stressors to maintain and restore disrupted cutaneous homeostasis. These complex functions are coordinated by a cutaneous neuro-endocrine system that also communicates in a bidirectional fashion with the central nervous, endocrine, and immune systems, all acting in concert to control body homeostasis. Although UV energy has played an important role in the origin and evolution of life, UV absorption by the skin not only triggers mechanisms that defend skin integrity and regulate global homeostasis but also induces skin pathology (*e.g.,* cancer, aging, autoimmune responses). These effects are secondary to the transduction of UV electromagnetic energy into chemical, hormonal, and neural signals, defined by the nature of the chromophores and tissue compartments receiving specific UV wavelength. UV radiation can upregulate local neuroendocrine axes, with UVB being markedly more efficient than UVA. The locally induced cytokines, corticotropin-releasing hormone, urocortins, proopiomelanocortin-peptides, enkephalins, or others can be released into circulation to exert systemic effects, including activation of the central hypothalamic-pituitary-adrenal axis, opioidogenic effects, and immunosuppression, independent of vitamin D synthesis. Similar effects are seen after exposure of the eyes and skin to UV, through which UVB activates hypothalamic paraventricular and arcuate nuclei and exerts very rapid stimulatory effects on the brain. Thus, UV touches the brain and central neuroendocrine system to reset body homeostasis. This invites multiple therapeutic applications of UV radiation, for example, in the management of autoimmune and mood disorders, addiction, and obesity. **(*Endocrinology* 159: 1992–2007, 2018)**

The sensory and computing capabilities of the skin are designed to control cutaneous and body homeostasis (1). Its structure, composed of epidermis, dermis, dermal adipose layer, and hypodermis (subcutaneous fat) with adnexal structures, innervation, vascular system, (neuro-) endocrine, immunological, pigmentary and metabolic activities, and bidirectional interaction of skin with the microbiome all serve the skin's central function as self-regulating protective barrier organ against an essentially hostile environment (1–3). Because this crucial interface organ also engages in thermoregulation, energy storage, and social communication (1, 4–8), these complex functions require coordination by both the local and the central neuroendocrine system (1, 8).

Given that UV light is a key determinant of life on Earth and that mammals exclusively come into contact

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Abbreviations: ACTH, adrenocorticotropic hormone; cHPA, central hypothalamic-pituitary-adrenal; CNS, central nervous system; CRH, corticotropin-releasing hormone; HPA, hypothalamic-pituitary-adrenal; MSH, melanocyte-stimulating hormone; NO, nitric oxide; POMC, proopiomelanocortin; TRPA1, transient receptor potential A1; UCA, urocanic acid; UVR, UV radiation; VIS, visible light.

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with UV via their integument and eyes (9), it is timely to reconsider the multiple different levels on which UV impacts via these two biological ports of entry not only on skin biology and pathology, but also on the organism as a whole—well beyond cutaneous physiology and pathology. Although the beneficial effect of UVB on vitamin D is well known (10–12) and therefore only discussed cursorily here, this review focuses on exploring the role of UV and, to a lesser degree, of visible light (VIS) in the regulation of central nervous system (CNS) and endocrine gland functions and overall body homeostasis.

Why Is UV Important?

The electromagnetic energy of solar radiation reaching Earth's surface encompasses infrared (700 nm to 1 mm), visible (400 to 700 nm), and UV (290 to 400 nm; shorter wavelengths, including UVC, are filtered by atmosphere), representing 53%, 44%, and 3%, respectively, of the ground level spectrum radiation of the sun in zenith (13, 14).

The biologically highly active UV spectra have played a fundamental role in the origin of life on Earth when simple organic molecules harnessed its energy and converted it into high-energy chemical bonds to generate molecular complexity (15–17), perhaps initiating self-organization patterns (18) (Fig. 1). In this context, it is important to mention that energy of UV is comparable to energy of covalent bonds. For instance, the carbonyl $\mathbf{n}\rightarrow\boldsymbol{\pi}^*$ transition (λ = 280 nm) demands energy of ~4 eV (*i.e.*, ~400 kJ/mol). It means that any electron excitement of a molecule with UV is enough to generate or break a covalent bond. In a biological system, it is also a supplemental way to support the cell with energy, while in the beginning of biogenesis—perhaps an important or even the only way. Under constant pressure and volume, this must lead to an increase of the total enthalpy of the system. The net negative change in the free enthalpy (Gibbs free energy) is the primary condition for the spontaneousness of a thermodynamic process. Such a process may have led to an increase of the inner-level organization (the self-organization) in the system. Therefore, it is not surprising that UV together with VIS has shaped biological evolution according to the laws of thermodynamics and promoted a diversity of organisms and species, including humans (16, 20, 21). Thus, the basic photochemical processes have not only defined the nature of biological responses but have also determined biological evolution according to the thermodynamic laws (Fig. 1). An example is the production of vitamin D2 from ergosterol (present in some of the earliest phytoplankton life forms) and vitamin D3 from 7-dehydrocholesterol after UVB-induced carbon-carbon bond cleavage (22).

Electromagnetic Energy of Solar Light Is Transformed Into Chemical Energy

The biologically relevant spectra of UV, which constitute major cutaneous stressors, include UVC (200 to 280 nm), UVB (280 to 320 nm), and UVA (320 to 400 nm) (1, 13, 23, 24). UVC is profoundly mutagenic, lethal, and is absorbed by the stratum corneum after irradiation by artificial light sources (24). UVB, while representing only a small fraction of Sun energy reaching Earth in the form of UV (5% of the total UV energy; *i.e.*, 0.03 × 0.05 = 0.0015 = 0.15% of the total solar radiation energy reaching Earth's surface), is very efficient at exerting biological effects and is absorbed mostly by the upper layers of the human epidermis, but also penetrates to the papillary dermis (13, 23). UVA has better penetration reaching the reticular dermis but has 1000 times lower efficiency at inducing biological effects (expressed as the minimal erythema dose) than UVB (25, 26). VIS deeply penetrates the skin reaching the hypodermis but it apparently does not inflict substantial photodamage, possibly due to a relatively poor absorption in the epidermis (9, 13, 23). The wavelengths of solar light reaching the Earth have similar photon energy (eV): VIS: 1.65 to 3.1, UVA = 3.10 to 3.94, UVB = 3.94 to 4.43 and UVC = 4.43 to 12.4 (http://www.spacewx.com/pdf/SET_21348_2004.pdf). This

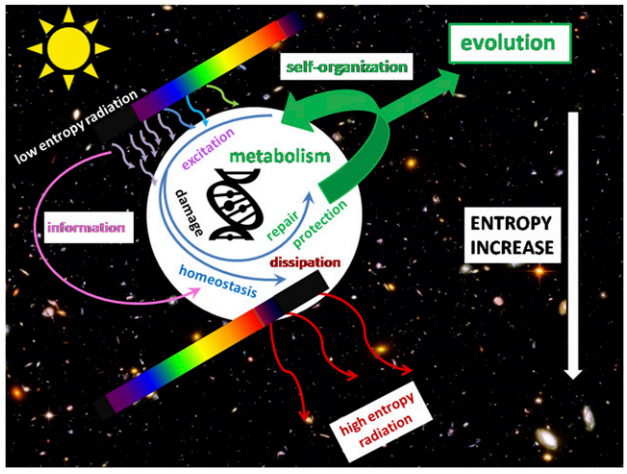


Figure 1. UV radiation as an initiator and driver of biological evolution. According to the second thermodynamic law, any self-organization must be driven by an irreversible process of energy flow in the form of low-entropy radiation from a container of high temperature (the Sun), and dissipate it in the form of high-entropy radiation in a container of low temperature (the space). UV radiation is enough to drive chemical reactions independently on metabolism and to damage the cell. DNA effectively dissipates the energy of excitation (19) and can store genetic information including only a limited number of UV-induced mutations. The cell also gets information on UV to set off the processes of repair and photoprotection, thus maintaining homeostasis, preserving enthalpy, and facilitating evolution. (The background: Hubble Deep Field; NASA, https://www.nasa.gov/. The DNA icon: PngTree, https://pngtree.com/free-icons.)

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indicates that magnitude of biological response is defined by nature of the chromophore and quantum mechanics of electron excitation.

In this context, most of biologically relevant chromophores such as compounds with a benzene ring including aromatic amino acids, biogenic amines, or proteins containing corresponding amino acids, pyrimidines, and purines with their derivatives alone or in nucleic acids, *trans*-urocanic acid (UCA), quinones, melatonin, indoles, melanin monomers, polymers and precursors, unsaturated lipids and 7-dehydrocholesterol as examples, absorb UVC and UVB, with surprisingly high absorption spectra in the UVC range (1, 10, 12, 13, 17, 20, 21, 23, 24, 27–29). Thus, the UVC signature may be a molecular record of the past, although UVB is highly relevant to the evolution of the integumental structures represented by the skin (1). In this context, UVB absorption by chromophores with their structural transformation to yield biologically relevant effects are of great importance (1, 13, 27, 30). In contrast, UVA, although it is weakly absorbed by DNA and by limited cellular chromophores (including NADH, reduced form of NADP, riboflavin, porphyrins), has the phenotypic effects that are mainly secondary to oxidative changes in the cells generated by reactive oxygen species (13, 23, 27). Another example is generation of nitric oxide (NO) from nitrosoglutathione (31) and photoreactivity of nitroxyl NO^- (32).

As it relates to VIS, its main retinal chromophore, in conjunction with opsin, is involved in phototransduction necessary for the vision and/or regulation of circadian rhythm (13). The flavins and pterines harvest shorter wavelengths of VIS and in conjunction with cryptochromes are involved in the photoreception and phototransduction and may affect circadian rhythm (13). Photogeneration of NO from nitrosoglutathione may contribute to the overall homeostasis of the organism, as NO, depending on the dose and the microenvironment, may act as a parahormonal regulator or neuromodulator/neurotransmitter, or a factor of oxidative/nitrosative stress (33). Concerning light-driven circadian rhythm, it can include induction of protective mechanisms necessary to counteract UV-induced damages during exposure to daylight, and for restoration of UV-disturbed homeostasis during night.

The Skin-Brain Axis Displays Major Neuroendocrine Activity

The skin is a recognized target for neuroendocrine signals delivered from circulation (hormones and neurohormones) or via nerve endings (neurotransmitters, neuropeptides, neurotrophins) that act on both resident and circulating cells of the skin through activation of specific membrane-bound and/or nuclear receptors (8, 34, 35). Examples of classical hormones or neuromediators generated by the central endocrine system regulating functions of the skin are adrenocorticotropic hormone (ACTH), glucocorticoids, mineralocorticoids, sex hormones, thyroid hormones, growth hormone, prolactin, various neuropeptides, neurotransmitters, and biogenic amines.

The phenotypic consequences of the signals exchanged between endocrine organs and the skin as well as between the brain, spinal cord, and the skin have been a subject of extensive reviews (1, 5, 8, 34–39) and thus will not be discussed in-depth here.

The skin operates as fully functional peripheral neuroendocrine organ

Because the initial recognition of the skin as the neuroendocrine organ involved in local stress responses that have systemic implications (8, 34), a substantial evidence has accumulated documenting the intracutaneous use of the same mediators and signal transduction pathways as the ones operating in the central neuroendocrine system [reviewed in (1, 4, 34–42)]. They include capabilities to produce on site variety of steroids (35, 42, 43), proopiomelanocortin (POMC)-derived peptides, corticotropin-releasing hormone (CRH), urocortins (34, 37), proenkephalin-derived peptides (1, 41, 44), endocannabinoids (45), catecholamines (46, 47), serotonin (48), melatonin (30, 49), thyroid-releasing hormone, thyroid-stimulating hormone, thyroid hormones (50, 51), acetylcholine (47, 52), oxytocin (53), adipokines (54), prolactin (55), growth hormone (56), and neurotrophins (57, 58). The complex interactions between these neuro-messengers and corresponding receptors in mammalian skin typically follow central regulatory paradigms of the hypothalamic-pituitary-adrenal (HPA) (59) and hypothalamic-pituitary-thyroid axes (50, 51, 54), prolactin (4, 60), or corticosteroidogenic (1, 36, 40, 61), cholinergic (52), opioid (41), biogenic amines (47, 48), melatonin (49, 62), and endocannabinoid (45) circuitries, complete with positive and negative feedback loops (Fig. 2). These interactions occur in addition to vitamin D formation and its activation through canonical (11, 12) and noncanonical pathways (43, 63, 64).

The skin immune system communicates with this diffuse neuroendocrine system in a bidirectional fashion using the same neuroendocrine messengers, cytokines, and cognate receptors, presumably to protect the local skin homeostasis against external stressors (1, 4, 8, 37). Release of soluble neuro-endocrine-immune factors into the circulation can exert systemic, endocrine, and CNS effects, as is impressively illustrated by UV radiation

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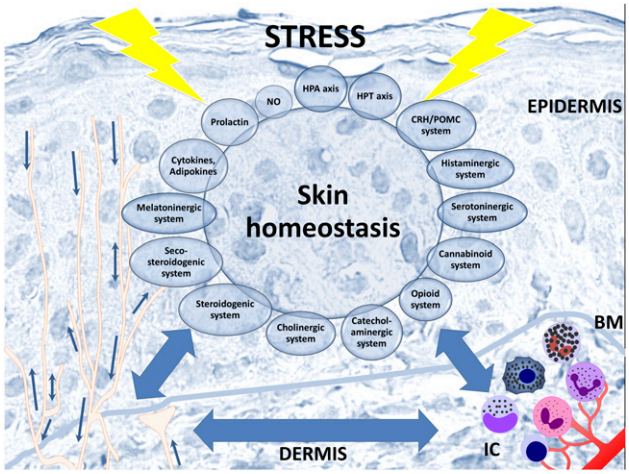


Figure 2. Skin neuroendocrine system. The skin neuroendocrine system integrates locally and centrally produced classical neuroendocrine or endocrine signaling molecules, thus providing a natural platform of interaction between internal organs and environment. To respond to a variety of internal and external signals, skin cells not only are sensitive to neurohormonal regulation but also produce elements of the HPA axis or hypothalamic-pituitary-thyroid axis, as well as other neuropeptides, biogenic amines, serotonin, melatonin, NO, opioids, cannabinoids, catecholamines, acetylcholine, steroids, secosteroids, and growth factors adipokines and cytokines. Skin's neuroendocrine system comprises epidermal and dermal cells including resident immune cells, nerve endings, and sensory receptors in the skin and its appendages. BM, basement membrane; IC, immune cells; HPT, hypothalamic-pituitary-thyroid.

(UVR)–induced β-endorphin (1, 65–67) and CRH (66, 68) releases from the skin, whereas immune cells that have been UV stimulated in the skin can act as cellular "second messengers" of the cutaneous neuro-endocrine-immune system to impact on global organismal homeostasis (Fig. 2).

NO and its donors (nitrosothiols) represent important hormonelike regulators of skin homeostasis; at the same time, NO is a mediator of the immunological, melanogenic, and neurologic effects of UV (69, 70). NO may be produced in both enzymatic and nonenzymatic fashion. There are three types of NO synthases encoded in various loci (71), and expressed in various skin cells according to the skin status (normal vs inflamed) (72) and the predominant phase of hair follicle cycling (73, 74). When produced in high amounts, NO itself becomes a nonspecific proinflammatory effector, and an important effector of oxidative/nitrosative stress (*e.g.*, by generation of peroxynitrite) (75).

NO may affect melanogenesis in both normal and malignant melanocytes (76, 77) and it potently regulates local blood flow in a paracrine manner (70). These NO-related effects strongly depend on UV. Importantly, blood-borne nitrosothiols such as nitrosoglutathione nonenzymatically release high amounts of NO upon action of UVA and short-wave VIS (31, 78). Thus, nitrosothiols serve as transient NO storage molecules and NO transport vehicles to distant body sites, executing the endocrine way of NO action. Under physiological conditions, Cu,Zn-dependent superoxide dismutase may reversely reduce NO to the nitroxyl anion NO^- (79). The latter is a chromophore for UV, and primarily undergoes phototransition to the singlet nitroxyl $^1NO^-$ isoelectronic with singlet oxygen $^1O_2$ (80).

Neuroendocrine communication within the skin-brain axis is bidirectional

Most skin components are innervated by the autonomic and/or somatosensory nerve fibers that transmit signals from and to the brain via spinal cord, cranial nerves, the sympathetic chain (paravertebral), and parasympathetic ganglia (8, 38). Moreover, direct spinocutaneous neural reflexes are established that do not require direct input from the brain (38). The classical sensory activities and routes of signal transmission including touch, pain, itch, temperature, stretch, and vibration are well established (38). Similarly, the descending pathways involved in the regulation of skin functions such as thermoregulation, sweat gland functions, blood flow, and other adnexal functions are also relatively well defined (38).

Although the importance of psychological factors in dermatology has long been recognized (81–83), psychodermatology as a field has recently witnessed a renaissance (84–87), not the least through improved understanding of how perceived (psychoemotional) stress aggravates or triggers skin pathology (*e.g.*, via the induction of neurogenic inflammation) (1, 5, 37, 38, 88–94). This growing body of knowledge is complemented by more recent insights into nonclassical skin sensory activities that encompass the sensing of defined biological (95–97) and physicochemical insults/stimuli, such as olfactory receptors or TRP mediated signals, VIS, and UV, which have been considered in skin physiology only relatively recently (1, 98–100).

Somatosensory nerves not only deliver signals from and to the brain through spinal cord or cranial nerves, but also form local networks transmitting signals between different skin compartments, adnexal structures, and the hypodermis, using ante- and retrograde reflexes, as discussed previously (8) (Fig. 3). For example, sensory nerve endings penetrate distal epidermal cell layers until immediately below the level of stratum corneum and innervate Merkel cells in both the epidermis, namely in tactile discs (Pinkus Haarscheiben), and the outer root sheath of the hair follicle, and densely innervated the bulge stem cell region of hair follicles (101–103). Thus, disturbances in the upper epidermis and hair follicle epithelium can be sensed and translated into electrical

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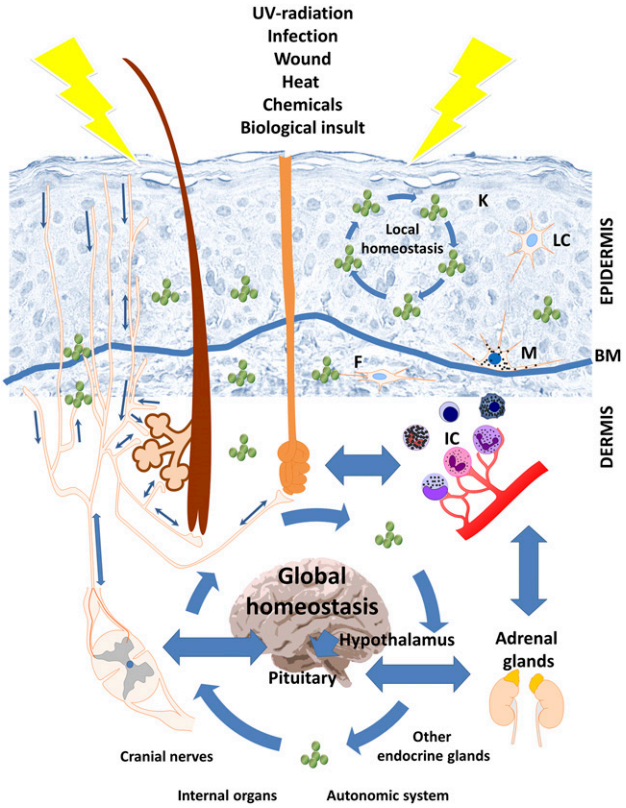


Figure 3. The interaction between the skin's endocrine system and central neuroendocrine system in stress response. The skin stress response system can activate central neuroendocrine responses with its direct homeostatic, metabolic, and phenotypic consequences. The crosstalk between local and central elements of stress response is maintained by bidirectional neuronal stimulation through naked nerve endings in the epidermis and innervation of adnexal structures (hair follicles; sebaceous, eccrine, and apocrine glands; arrector pili muscle). Active neuroendocrine mediators could also be directly secreted in response to stimuli by neurons, epidermal keratinocytes, melanocytes, and Langerhans cells, as well as dermal residing mast cells, macrophages, and fibroblasts or infiltrating lymphocytes and granulocytes. Furthermore, the circulatory system provides an additional route for an exchange of signaling molecules between the skin's neuroendocrine system and central endocrine organs, including elements of the HPA axis. Constant exchange of neuroendocrine mediators between skin and other organs is responsible for the maintenance of local and global homeostasis and skin response to external and internal signals. BM, basement membrane; F, fibrocytes/fibroblasts; IC, immune cells; K, keratinocytes; LC, Langerhans cells; M, melanocytes.

impulses that are rapidly transmitted to the spinal cord or via retrograde reflex arches leading to enhanced intracutaneous release of neuropeptides, neurotransmitters, and/or neurotrophins from sensory nerve fibers as proposed originally (8).

These sensory innervation pathways can also activate nerve fiber-associated mast cells that appear to play a key role as "central switchboards" of neurogenic inflammation, setting off a proinflammatory chain of neurogenic skin inflammation events that also impacts on other intracutaneous immunocytes (104–107), and can even have systemic immunomodulatory effects (Fig. 3). Interestingly, it is known that the skin generates electrical fields under conditions of wound healing and that, *vice versa*, electrical stimulation can promote both wound healing and the induction of neural differentiation markers (108).

Therefore, it is also conceivable that local activation of the endothelium of the papillary dermis plexus might transmit an electric current to the deep dermal or hypodermal plexuses, because these plexus form one continuum resulting in phenotypic activities and/or release of soluble mediators (Fig. 3).

UVR regulates body homeostasis via activation of the central neuroendocrine system

Because the original concept that mammalian skin harbors peripheral equivalent of the central HPA (cHPA) (109), which was further developed into the concept that HPA organization was first developed in the integument during evolution and was only later adapted by the central neuroendocrine system (110), substantial evidence has accumulated that strongly supports the notion that skin and its appendages are using molecular elements of the HPA to coordinate responses against stressors [reviewed in (4, 5, 37, 59, 104, 111–116)].

UVR stimulates both the intracutaneous and the cHPA axis

However, although on the central level, all regulatory elements of the HPA (hypothalamus, pituitary, adrenal glands, cytokine signaling) are anatomically separated and have a linear hierarchy (117, 118), these exist in close proximity to each other and often even within the same epithelial cells of mammalian skin, thus securing nonlinear interactions that are evolutionary conserved (1, 4, 5, 37, 110). Therefore, in principle, the local CRH/urocortin (119–121), POMC-signaling axes including the POMC-derived peptides such as α–melanocyte-stimulating hormone (MSH), β-endorphin, and ACTH (34, 122), and the cutaneous steroidogenic systems (43, 61, 123) all can act both individually and in concert to regulate local tissue homeostasis (4, 35, 37). A disruption in these interactions may result in skin pathology, as has recently been demonstrated for psoriasis (1, 5, 36, 37, 104, 111, 112, 124–126).

UVB can upregulate α-MSH receptor (MC1R) expression and activity (127, 128), POMC expression, and POMC peptide production including that of α-MSH, β-endorphin, and ACTH (127, 129–131), presumably to regulate mammalian skin pigmentation, to protect skin from UV induced injury, and to modulate skin immune responses (1, 34, 122, 128, 132–135). UVB also stimulates CRH and urocortin production (131, 136–138) and changes CRH receptor type 1 (CRH-R1) expression

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pattern and activity (139–141), all to restore local homeostasis and to build protection against UVB damage (1, 37, 142). However, only recently it has been demonstrated that UV can simultaneously stimulate all elements of the cHPA including glucosteroidogenesis (66, 131, 136, 143). This stimulation is dependent on wavelength with the shortest spectrum UVC having the strongest effect, followed by UVB, whereas UVA has no or minor effects restricted to increases of CRH and β-endorphin peptides (131, 136).

Importantly, the exposure of shaved back skin of C57BL/6 mice to UVB significantly stimulates cHPA axis activity already 12 and 24 hours after irradiation (66). Moreover, UVB enhances skin and plasma levels of CRH, urocortin, β-endorphin, ACTH, and corticosterone levels, along with simultaneous stimulation of *CRH* gene and protein expression in the paraventricular nucleus of the hypothalamus and of *MC2R*, *StAR* (steroidogenic acute regulatory protein), and *CYP11B1* genes in adrenals. Because hypophysectomy abolishes UVB stimulation of plasma, but not of skin corticosterone levels, and has no effect on UVB stimulation of CRH and urocortin, this documents that the regulation of body homeostasis by UVB through the cHPA axis requires an intact pituitary for systemic effects.

This systemic stimulation of POMC peptides and corticosteroidogenesis by UVB provides a plausible endocrine mechanistic explanation of the well-known phenomenon of systemic immunosuppression by UVB (144), which was traditionally thought to be secondary to changes in the keratinocyte cytokine signaling milieu and a result of immunosuppressive T-cell activities (14, 144, 145). These systemic immunosuppressive effects appear to be independent from the UVB-induced production of vitamin D (145, 146). As a consequence, stimulation of the local and systemic HPA axes or their individual elements (POMC signaling and steroidogenesis), which encompass both chemical mediators, and stimulation of cognate receptors must play an important but long neglected role in intracutaneous or systemic immunosuppression.

In parallel, the Hiramoto group (147–150) reported remarkable systemic effect of exposing the eyes of C57BL6 mice to UVB, which increased the serum levels of α-MSH (147–149), ACTH, CRH, and urocortin 2 (149, 150) within hours after the UVB exposure. Hiramoto *et al.* (147) proposed that this systemic neuroendocrine UVB effect is mediated through stimulation of the hypothalamic pituitary axis in an NO-dependent manner through the ciliary (parasympathetic) ganglia involving the first branch of the trigeminal nerve (ophthalmic) but not through the optic nerve. Thus, UVB can activate cHPA or its elements both through the skin and/or via the eye (98). Furthermore, irradiation of the eye by UVA led to the stimulation of systemic α-MSH, ACTH, and β-endorphin with downstream immunosuppressive effects (150–152), with signal transmission to the brain involving optic but not trigeminal nerve (151). Thus, even eye-transmitted systemic neuroendocrine effects, at least to some extent, can be regulated by cutaneous structures that impact the ocular transmission of UVB energy.

In this context, one should not forget that UVB energy can be absorbed by lobular, fornical-orbital, and tarsal conjunctiva and by adjacent connective tissue as well as posterior and intermarginal cutaneous elements of the eyelid, all of which represent integumental structures (98).

Interestingly, irradiation of the ear also enhances POMC-derived α-MSH blood levels (147–149), consistent with UVB activation of central POMC activity through the skin (66–68). Our own data also indicate involvement of neural signal transmission from the skin to the CNS with partial deviation from classical HPA paradigms, as documented by the rapid stimulation of brain and plasma CRH, β-endorphin, ACTH, and corticosterone levels 30 and/or 90 minutes after UVB exposure, with hypophysectomy having no effect on UVB-induced increases of systemic corticosterone (68). In summary, UVR can thus regulate entire or selected elements of the cHPA axis through neural and humoral mechanisms that are wavelength-dependent and defined by anatomical structures sensing UV energy.

Stimulation of the central POMC and related systems exerts downstream homeostatic effects

Recently, the hypothesis that UV can even regulate internal organ functions through the brain or spinal cord reflexes (8) has received experimental support (67, 68). Specifically, exposure of back skin to the UVB stimulated the expression of *Pomc* and *MC4R* messenger RNAs in the hypothalamus with concomitant inhibition of *AgRP* in a time- and dose-dependent fashion. The effect on *Pomc* was seen as early as 1 hour after exposure to UVB (67). These changes in gene expression were accompanied by more α-MSH and MC4R-immunoreactive neurons in the arcuate nucleus as well as by increased brain and plasma levels of α-MSH and β-endorphin (67). It was suggested that this route of stimulation might link UVB with the central regulation of body metabolism and feeding behavior (67).

This surprising discovery was supplemented by the finding that UVB-exposure rapidly (*i.e.,* after 30 and 90 minutes) increases of CRH and β-endorphin levels in the brain and plasma; furthermore, ACTH and corticosterone plasma levels were quickly raised, as were adrenal *StAR* and *CYP11B1* gene expression (68). Thus,

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UVB can also rapidly activate the POMC system in the brain, followed by the release of centrally derived POMC peptides into the circulation, in the manner that is separate and distinct from the HPA axis.

The UVB reception in the skin not only activated central neuroendocrine pathways, but also induced rapid systemic immunosuppressive effects, which showed an extended duration, as illustrated by inhibition of Th1 and Th2 activities in the spleen 30 and/or 90 minutes after UVB exposure that lasted for at least 24 hours (68). The concomitant rapid stimulation of systemic CRH, ACTH, β-endorphin, and corticosterone, accompanied by rapid immunosuppressive effects on splenocytes appeared to be independent of the cHPA axis (68). The proposed mechanism includes rapid transmission of the signal via the ascending and descending autonomic nervous system pathways of the spinal cord (*e.g.,* preganglionic intermediolateral nucleus) to influence several nodes of the brains' autonomic control network (*e.g.,* amygdala, hypothalamus, periaqueductal gray matter, raphe nuclei, and selected brainstem nuclei) and subsequently, may have result in an activation of corticosteroidogenesis in adrenal cortex and sympathetic inhibition of immune activity in the spleen (68).

The Hiramoto group (147–157) has also shown that exposure of the eye to the UV not only activates central (pituitary) POMC-signaling system in a wavelength-dependent manner (UVB vs UVA) that uses NO signaling, but also has distinct functional effects on internal organs and the skin depending on times postradiation varying substantially between 6 hours (151, 152), several days (149, 153), and 20 weeks (157) after UVR-exposure. These authors showed stimulation of cutaneous melanocytes by UVB-induced α-MSH (147, 149), downregulation of cutaneous Langerhans cells by UVA (151), deterioration of dextran sodium sulfate-induced ulcerative colitis by UVB and its improvement by UVA (150), and amelioration of atopic dermatitis by UVA (156). Moreover, they reported amelioration of colon carcinoma induced by azoxymethane and dextran sodium sulfate through UVA stimulation of β-endorphin and methionine-enkephalin (157) and modulation of mucosal intestinal functions by UVA (153).

The proposed mechanism for these UV-induced effects involves activation of the hypothalamic-pituitary (147–149, 151) or HPA axis (152). Although the requirement for intact optic nerve function in UVA induced signal transmission (151) suggests a critical involvement of the retina in this process, lack of such requirement for UVB (147) indicates an involvement of integumental structures connected with the eye (*e.g.,* conjunctiva and eyelid) (98). Interestingly, repeated UVB exposure of the skin can negatively affect hippocampal neurogenesis and synaptic plasticity along with HPA axis activation (158).

UV stimulates the opioidogenic system

The UVB stimulated β-endorphin levels in the skin (66, 131, 143), plasma (65–68), and brain (66–68) can be linked to the phenomenon of "UVB addiction" (65, 159, 160) as well as to nociceptive and other behavioral effects (1, 65, 67). It has been hypothesized that these UVB-induced, β-endorphin-dependent behavioral and POMC pigmentary activities are regulated by p53 (65, 161). This requires independent confirmation, because there is no p53 responsive region in the POMC gene and because C57BL6 mice (*i.e.,* model used in these studies) produces eumelanin constitutively without requirement of POMC (162, 163). In any case, that UVB can stimulate β-endorphin production not only in the skin (66, 131, 143), but also in the brain shortly (68) or after longer time periods post exposure (66, 67) identifies an exciting area for future research into how light "touches" the brain.

UVA also stimulates β-endorphin in the skin (131) and colon with concomitant increases of methionine-enkephalin and attenuation of colonic carcinogenesis (157). This not only documents that UVA can exert an opioidogenic effect (1, 41) but also that this may have selected beneficial health effects (157). Concerning enkephalins, it has been demonstrated that UVB can stimulate proenkephalin gene expression in skin cells in a dose- and time-dependent manner (44).

UVB exerts indirect effects via vitamin D actions

The pleiotropic effects of vitamin D including endocrine activities are well documented and extensively reviewed (10–12, 164, 165). The effects of active forms of vitamin D on brain functions including regulation of biogenic amines levels (166, 167) and neurosteroidal activity (168) are being gradually appreciated. Recent evidence documents an involvement of vitamin D in the upregulation of tryptophan hydroxylase type 2, with enhancement of brain serotonin exerting complex behavioral effects (169–171). Furthermore, it has been demonstrated that $1,25(OH)_2D3$, and recently discovered noncalcemic vitamin D analogs (43, 172, 173), can stimulate the expression of CRH, urocortins, and POMC, and their receptors, CRHR1, CRHR2, MC1R, MC2R, MC3R, and MC4R in human skin (174). Thus, active metabolites of vitamin D could contribute indirectly to the UVB induced behavioral effects or may impact the stimulation of the HPA and/or CRH and POMC-signaling systems in the periphery or at the central levels.

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Major Open Questions and How to Address Them

One of the most intriguing and challenging current questions is whether human skin can sense and transform VIS into organized local and central responses represents a challenging question, because of the central function of the eye in the photoreception and central regulation of circadian rhythm.

The skin has eyelike photosensory system

One can argue that such system should operate as a conserved mechanism employed by invertebrates and lower vertebrates who use melanopsin and invertebrates opsins for light sensitivity outside the eye (175–177). This mechanism could overlap with the cutaneous UVR reception system as previously predicted (128, 178). In fact, experimental evidence is accumulating for the establishment of cutaneous photosensory mechanisms composed of different light-sensitive opsins, namely rhodopsin, melanopsin, neuropsin, and encephalopsin and photosensitive circadian clock proteins (179–183). Activation of these photosensory systems in skin and skin cells by visible or UVA light leads to measurable phenotypic effects (184–186) of which the best characterized is melanin pigmentation (180, 187–189). For example, it has been proposed that UV phototransduction in melanocytes involves a retinal-dependent signaling cascade that involves the activation of a Gαq/11-dependent phosphoinositide cascade, which resembles phototransduction in the eye (190). This UV reception mechanism involves the activation of transient receptor potential A1 (TRPA1) ion channels (190–192).

Perhaps, the greatest experimental challenge in dissecting this cutaneous photosensing system is how to distinguish VIS from UV effects and to define the relevant pathways, because UV lamps contain also VIS spectra. It also relates to the regulation of the local circadian rhythm and its communication with the local neuroendocrine systems (193) including serotoninomelatoninergic pathways (30, 48, 49). Furthermore, the skin is rich in pterines, light chromophores, and has an efficient system for their *de novo* synthesis and recycling, which are important not only for local phenotypic effects and homeostasis but also for the local synthesis of biogenic amines (194–198). This raises additional questions on the wavelength-dependent detection of solar light energy by the skin with its translation into precise signal transduction pathways affecting local and systemic neuroendocrine systems. In addition, the recently described discovery shows the prosurvival effect of infrared A spectrum of solar radiation on UV-damaged human melanocytes (199, 200). Also melanocytes and keratinocytes show distinctive responses to UVR (201), and different spectra of light have different effects on free radical formation and lipid composition in the skin (202).

How absorption of the UV energy by the skin is translated into central neuroendocrine activities

Another key problem is how to dissect direct UVR effects from indirect ones and their further downstream signaling. The direct effects are secondary to the absorption of UV energy by specific chromophore(s) in a wavelength-dependent manner, followed by conformational changes of the interacting protein (light receptors). The latter effects also include the direct activation of sensory nerve endings via UV-induced changes in the physicochemical environment (*e.g.*, pH, temperature, free radicals, local ion concentrations) of the exposed nerve ending or its close vicinity. Alternatively, depolarizing cell membrane damage could result in electrical impulses that are transmitted after reaching activating threshold (8, 178).

Interestingly, in planarians TRPA1 can be activated by reactive oxygen species indicating a conserved mechanism for animal nociception induced by physicochemical factors (203). Therefore, it is conceivable that the specificity of UV responses may be enhanced by the receptors coupled to ion channels, such as members of TRP family including TRPA1. In addition, UV can directly activate TRPA1 via the chromophore retinal in melanocytes (190–192), cells of neural crest origin.

Another important question is which chromophores have appropriate protein partners in skin cells or nerve endings that trigger signal transduction pathways, which then translate the frequency of electromagnetic energy into chemical messengers. In this scenario, the nature of the chromophore with its absorption of a defined frequency of electromagnetic radiation would define the specificity for UVB, UVA, or VIS responses. A classical example is 7-dehydrocholesterol, which after absorption of UVB photoisomerizes to previtamin D (10, 12). UCA is another chromophore, whose photoproduct, *cis*-UCA, although being a potent immunosuppressor (204), can also interact with serotonin receptors (205–207). Also, tryptophan photoproducts can interact with the aryl hydrocarbon receptor (208–210). Moreover, UVB absorption by DNA resulting in DNA damage concomitantly stimulates pigmentation and both expression and activity of POMC (211, 212) as an indirect effect of UVR (1). Finally, the contribution of lipids in UV transduction must not be underestimated in this context, given their paramount role in epidermal barrier functions (2, 3) and predominant absorption of short UVB wavelengths by the stratum corneum with lower penetration to stratum granulosum (9, 23, 24).

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The indirect chemical messengers for UVR include local neurohormones produced and released by skin cells (*e.g.,* ACTH, α-MSH, β-endorphin, CRH, urocortins, enkephalins, cytokines, steroids, and others) [reviewed in (1, 35, 37)]. Their local and systemic effects would be defined by cell types producing such messengers, and their spatial location including proximity to blood vessels and nerve endings. The former will secure entry of soluble mediators into the circulation (8), whereas the latter will include rapid transmission to the CNS once locally produced enkephalins, β-endorphin, α-MSH, serotonin, or other neurohormones bind to the receptors expressed on cutaneous nerve endings (8). It must be noted that sensory nerves express opioid, cannabinoid, MC1, serotonin, and other receptors for locally produced neurotransmitters and neuropeptides as well as cytokine receptors (38, 41, 96, 97, 104, 133). The future challenge is to map such receptor expression in sensory nerves in relation to their anatomical and spatial distribution within human skin, along with measuring the subsequent central input after intracutaneous receptor stimulation, preferably by noninvasive brain imaging techniques such as functional magnetic resonance imaging or transcranial magnetic stimulation (88).

The downstream signaling will include stimulation of endocrine organs (39) or systemic immune system (213–215) secondary to UV-induced entry of humoral signals to the circulation (CRH, urocortins, POMC-peptides, cytokines, serotonin, melatonin) or the organ activation via neural transmission through somatosensory and autonomic system with signals originating from or bypassing brain (1, 8, 30). The downstream signaling will be represented by endocrine activities of the pituitary, adrenal glands, and possibly other glands such as thyroid, pancreas, and gonads, which will regulate body homeostasis and metabolic activities. The final effectors will be internal organs (*e.g.*, GI tract, liver, spleen, kidney, or lungs) with their changed activities secondary to UV exposure of the skin.

The final challenge is to define which skin cell type would act as the main system that senses and computes UV energy and then translates this into defined biological responses in the cutaneous neuroendocrine concert. Besides UV-sensitive keratinocytes, other obvious candidates are melanocytes that can sense UV and respond to it through melanogenesis, synthesis, and release of neurohormones and cytokines; moreover, melanocytes can engage in direct cell–cell contact via their UV-stimulated network of dendritic processes that communicate with multiple cellular targets as proposed previously (216–219) (Fig. 4). In the dermis, instead, UV-sensitive mast cells (221–223) may operate as master regulators that translate light energy into biological

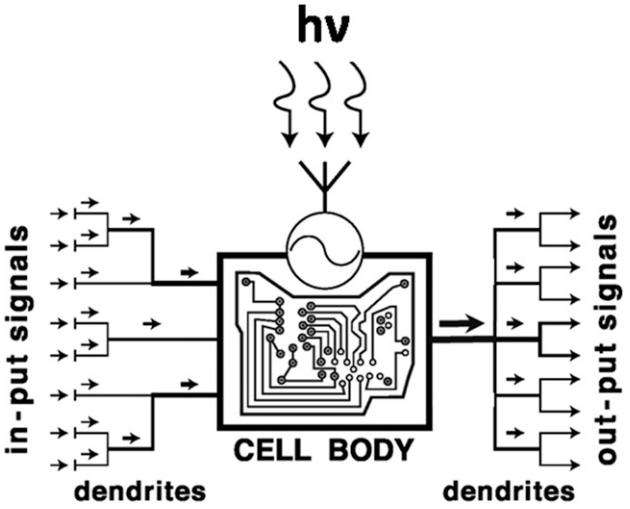


Figure 4. Melanocyte as the computing UV sensor, effector, and master regulator in the epidermal neuroendocrine concert. Melanocytes—melanin-producing cells with neuroendocrine capabilities (122, 218)—after receiving UV electromagnetic waves, decode them according to their frequency, translate the absorbed energy/information into biologically relevant signals and activities, and convey them to multiple effector targets (217, 218). The UV-induced formation of multiple dendrites (122, 128, 212, 220) allows them not only to amplify the biological effect (right, output) but also to enhance the capability of sensing UV-induced disturbances in epidermal homeostasis by collecting information from multiple structures at different, sometimes distant spaciotemporal locations (left, input). hv, a quantum of UV irradiation.

responses (104, 223). Given that, in murine skin with synchronized hair follicle cycling, numerous cutaneous functions, ranging from pigmentation via type IV immune and photoallergy responses to neuroendocrine activities and wound healing, show major hair cycle-associated fluctuations (4, 224–229), the hair follicles also impact profoundly on cutaneous responses to UVR.

Afferent neuronal UV-induced signaling pathways may originate in skin

Although the sensory innervation of the skin is well characterized (1, 38, 230, 231), there is lack of satisfactory information on what type of sensory nerves are UV responsive, and where, how, and via which neural route UV-induced signals are transmitted. It is likely that signal transduction will be dependent on neuroanatomical differences in skin innervation (*e.g.,* between head/neck, torso, and extremities). Another main challenge in this context is to determine which crucial coordinating brain structures are activated in addition to hypothalamus (66–68, 147, 151), including arcuate nucleus and paraventricular nucleus (66–68), and through which communicating network the UV-induced signals follow (98). It is also unclear which effector systems (sympathetic or parasympathetic) are activated and which UV-induced spinal or extraspinal neural circuits can bypass the brain to directly target immune organs such as the

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spleen (68) and other internal organs (98, 150, 153, 157). These questions remain open because experiments on mice, a nocturnal species with distinct neurobiological characteristics, may provide only limited information that is directly transferable to humans (1, 35, 37).

Conclusions and Future Directions

Because UV energy has shaped both biological evolution and homeostatic responses, it is not surprising that UV regulates global homeostasis after absorption and transduction of its electromagnetic energy into chemical, hormonal, and neural signals in a wavelength-dependent fashion, defined by its tissue penetration and the nature of the chromophores UVR interacts with. This homeostatic activity includes activation of the CNS and/or endocrine glands through neural transmission or chemical messengers originating in the skin. This type of regulation, although representing relics from earlier periods of biological evolution, follows precise neuroendocrine regulatory mechanisms of which examples are represented by HPA, CRH-POMC, opioidogenic, serotonin/melatoninergic, secosteroid/steroidogenic, or NO systems.

In dermatology, phototherapy is used to treat inflammatory, pigmentary, and other skin disorders (23, 87). Phototherapy includes direct use of UVB or UVA, psoralens with UVA, or various combinations thereof. An increasing range of dermatoses and cosmetic skin conditions may also be amenable to phototherapy with VIS (232–234). Thus, with the increasing application of UVR and VIS to human skin, it becomes ever-more important to understand how exactly UV and VIS light "touch" the brain along the routes synthesized in this review, and to which extent the clinically desired outcomes of UV therapy reflect secondary phenomena that result from resetting the body homeostasis through activation of central neuroendocrine pathways.

That phototherapy also may hold promise in the treatment of selected systemic autoimmune diseases such as rheumatoid arthritis, inflammatory bowel diseases, multiple sclerosis, and scleroderma (59, 66, 68, 150, 152) all of which renders the need to better understand the UV-skin/eye-brain axis discussed here even more pressing. This is further underscored by emerging evidence that UV therapy may also be used in treatment of chemical addiction and in mood disorders due to its opioidogenic effects (1, 44, 65–67), and that UV may even be employed to regulate body metabolism, food intake, and appetite via its effects on POMC, CRH, and agouti-related protein signaling (67, 98).

Thus, we have long entered into an exciting new territory of endocrinological research that may perhaps best be termed "photo-neuroendocrinology" and is just waiting to be systematically explored and therapeutically targeted.

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