

Neuroendocrine Aspects of Skin Aging

Subjects: **Dermatology**

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Skin aging is accompanied by a gradual loss of function, physiological integrity and the ability to cope with internal and external stressors. This is secondary to a combination of complex biological processes influenced by constitutive and environmental factors or by local and systemic pathologies. Skin aging and its phenotypic presentation are dependent on constitutive (genetic) and systemic factors. It can be accelerated by environmental stressors, such as ultraviolet radiation, pollutants and microbial insults.

skin aging

melatonin

vitamin D

photoprotection

1. Introduction

The skin is a complex multifunctional self-regulating organ in the human body. Its functions are critical to survival. The skin is not only a barrier that protects the organism from the deleterious insults of the external environment, but it is also crucial for thermoregulation, as well as its maintenance of electrolyte and fluid balance. Moreover, the skin also responds to environmental changes, such as biological, chemical, and physical factors, in order to regulate cutaneous and global body homeostasis ^{[1][2][3]}.

It is well established that in the skin there is an important sophisticated network connecting cutaneous nerves and the local neuroendocrine and immune systems. The brain directly (via efferent nerves) or indirectly (via the adrenal glands or immune cells) regulates skin function. The neurocutaneous communication comprises of afferent and efferent nerves that release mediators acting on corresponding receptors expressed on skin cells ^{[1][4]}. Furthermore, as a sensory organ with neuroendocrine activities, the skin can also transmit humoral or neuronal signals to the central nervous, endocrine and immune systems. In addition, environmental factors or pathological processes induce skin changes that can imprint circulating immune cells acting as cellular messengers of skin responses to the changes in local homeostasis ^{[1][2]}. The skin also operates as a biofactory for the synthesis, processing and metabolism of the wide range of structural proteins, glycans, lipids and signaling molecules ^[5], as well as a fully functional neuroendocrine organ ^{[6][7]}. The human skin produces a variety of hormones, neuropeptides and neurotransmitters ^{[1][2][3][8]} in addition to the formation of vitamin D3 ^{[9][10][11]}. The skin responds to stress (such as UV light) by local synthesis of all hormones of the classical hypothalamic-pituitary-adrenal (HPA) axis ^[12]. Specifically, skin cells are capable of producing corticotropin-releasing hormone (CRH) ^{[13][14][15][16][17][18][19][20][21]}, CRH-related peptides including urocortin 1 and 2 ^{[3][22]}, proopiomelanocortin (POMC)-derived ACTH, α -MSH and β -endorphin ^{[3][13][23][24][25][26][27][28]}, and glucocorticoids ^{[29][30]}. They also express the corresponding receptors. There are also many other hormones synthesized or activated/inactivated in the skin, including thyroid releasing hormone (TRH), thyroid stimulating hormone (TSH) and thyroid hormones, ^{[31][32][33][34]}; sex hormones

and their precursors, as well as Δ^7 steroids and different secosteroidal products [7][29][35][36][37][38]. The skin expresses the enzyme cytochrome P450scc (CYP11A1), which initiates steroid synthesis by converting cholesterol to pregnenolone in a similar manner as in other steroidogenic tissues [36][38][39][40][41][42][43][44][45]. In addition, skin cells can produce catecholamines [46][47], serotonin [48][49][50][51], and melatonin [48][50][52][53][54][55]. Indeed, melatonin and its biologically active metabolites are essential for physiological skin functions and protection against environmental stress [48][54][55][56][57][58].

2. Skin Aging

Aging is a natural process leading to the accumulation of damage and progressive deterioration in the biochemical, physiological and morphological functions on the systemic or organ levels [59][60]. Chronobiological aging mainly results from imbalanced endocrine circadian rhythmicity, which is linked to numerous health complications and pathologies in aging populations. Many factors can cause or aggravate hormone deficiencies (like nutritional, dietary, lifestyle, behavioral, environmental deficiencies, etc.) [61][62]. These hormonal changes induce morphological and functional alterations of all organs and systems, including the central nervous system (CNS) and skin. Moreover, the physiological aging process results in most of the phenotypic changes observed in the skin. There are age-related changes affecting all endocrine glands, which sometimes are so intertwined that the reduced function in one gland affects the other one [2][7][63]. Aging affects the expression of POMC and production of POMC-derived peptides, especially of melanocortin receptor 1 (MC1R) and MC2R agonists, which are of crucial importance for skin biological systems [2][64]. The regulation of the skin steroidogenic system cannot be underestimated, since it can regulate epidermal functions and skin immunity [7][38]. The breakdown of this steroidogenic activity can lead to pathological skin changes and diseases. The abnormal synthesis of skin cholesterol, involving a drastic reduction in steroids, is associated with down-regulation of epidermal differentiation [7][38][65]. Furthermore, the levels of steroidogenic acute regulatory protein (StAR) mRNA were found to gradually decrease in the skin tissues of elderly people, in contrast to younger ones [66]. With increasing age, the capacity of the skin to produce vitamin D₃ declines, thus its protective effects are reduced [67][68]. Several factors contribute to this vitamin D deficiency state, such as behavior factors (limited sun exposure, malnutrition, etc.) and reduced synthetic capacity [69].

3. Anti-Aging Strategies

While aging as a natural phenomenon is genetically determined, premature photoaging can be prevented. Wrinkling and pigmentation are directly associated with premature skin aging and are considered to be the most critical skin events [70]. Photoprotection achieved by physical and chemical UV filters is the main preventive measure against skin photo-damage. Use of nutraceuticals (the term is derived from “nutrition” and “pharmaceutical” [71]) represent a promising strategy for preventing, delaying or minimizing the premature skin aging and age-associated diseases, including skin cancers [72]. Among them are plant polyphenols, bioactive peptides and oligosaccharides, carotenoids, vitamins and polyunsaturated fatty acids. Although some studies have reported that polyphenols can exert cytotoxic effect, polyphenolic compounds (curcumin; polyphenols from green

tee, grape, soybeans, pomegranate, etc.) belong to the most frequently used ingredients in modern cosmeceutical and dermatological products [73][74][75][76][77]. Numerous studies suggest that polyphenols modulate the cellular inflammatory response of the NF- κ B pathway [78][79] and exert indirect antioxidant actions via activation of the Nrf2 [80].

Topical nicotinamide (niacinamide, vitamin B3) improves skin appearance and provides beneficial effects in prevention of the loss of dermal collagen that characterizes photoaging [81][82][83]. Vitamin B₃, a precursor of Nicotinamide Adenine Dinucleotide (NAD), can also prevent UV-induced depletion of ATP in keratinocytes, leading to the acceleration of energy-dependent DNA repair processes [84]. When DNA damage cannot be repaired, an activation of poly-ADP-ribose-polymerase (PARP-1) induces apoptosis by activation NF- κ B pathway [85]. Hence, the UV-protective effects of vitamin B₃ on the skin include regulation of cellular metabolism [86][87]. The ability of nicotinamide to enhance PARP-1 and regulate DNA repair mechanisms lead to its inclusion in regular sunscreens [88][89].

The potent antioxidant properties of vitamins C and E are well known and documented. They are widely used for skin care and in photo-protection, either as nutraceuticals or for topical application [90]. The incorporation of ferulic acid improves chemical stability of the vitamins (C + E) and increases photo-protection of photo-exposed skin [91][92][93].

Another preventive measure against premature skin aging is the usage of vitamin D3 derivative_s. It was reported that active forms of vitamin D3 protect, attenuate, or even reverse UVB-induced cell and DNA damage in skin cells [67][94][95][96][97][98][99][100]. Unfortunately, the chronic use of vitamin D3 at therapeutic doses in its classical active forms including 1,25(OH)₂D₃ is severely limited due to its calcemic (toxic) effects. However, the discovery of an alternative pathway of vitamin D activation initiated by CYP11A1 [36][37][38], which produces biologically active but non-calcemic novel derivatives detectable in vivo [101][102][103][104], offers promises for therapeutic applications against photoaging and UVR induced skin pathology [105]. Vitamin D analogs may increase the DNA repair capacity in keratinocytes and melanocytes by enhancement of the expression of tumor suppressor protein p53 phosphorylated at Ser-15, but not at Ser-46 [106]. Phosphorylation at Ser-15 and Ser-20 of p53 activates p53 and promotes DNA repair, with phosphorylation of p53 at Ser-46 being responsible for regulation of apoptosis after DNA damage [107]. In addition, novel vitamin D derivatives produced by CYP11A1 down-regulate the formation of mutagenic and genotoxic cyclobutane pyrimidine dimers (CPD) produced after UVB exposure.

Thus, both classical 1,25(OH)₂D₃ [95][96] and novel CYP11A1-derived 20(OH)D₃ and 20,23(OH)₂D₃, and other vitamin D3 derivatives, may work as protectors of the human epidermis against UV-induced oxidative damage, not only in keratinocytes but also in melanocytes [106].

Vitamin D3, production of which in the skin is induced by solar radiation, is essentially important as a protector of skin homeostasis [108]. It can attenuate DNA- and metabolic-damage by reducing H₂O₂ and NO levels, elevating glutathione levels, and enhancing DNA repair. In advanced age, the capacity of the skin to produce vitamin D,

which could be a part of this intrinsic protective mechanism against UV-damage, declines. Therefore, the supplementation of vitamin D is of great importance in the elderly population.

The most promising candidate for delaying skin aging and for the treatment of several dermatoses associated with oxidative damage is melatonin. Melatonin is the main secretory hormonal product of the pineal gland and a regulator of chronobiological activities. Melatonin is also synthesized in numerous extrapineal sites including skin and hair follicles [54][58][109][110] where it can act on functional melatonin type 1 and 2 receptors (MT1 and MT2) [48][53][111][112][113][114][115]. Surprisingly, it was found that skin produces a much higher amount of melatonin for its own use than can be detected in serum [54][110]. Skin melatonin exerts multifaceted functions [114][115]. In addition to receptor-mediated actions, melatonin and its metabolites act as relevant direct antioxidants. Moreover, melatonin is one of the most potent free radical scavengers [116][117][118], even stronger than vitamins C and E [119]. Several in vitro studies have confirmed that melatonin and its metabolites can protect keratinocytes and melanocytes from UVB-induced damages. The mechanism of this protection includes activation of Nrf2 and upregulation of the Nrf2-related pathway [120][121]. Similarly, melatonin protects dermal fibroblasts from solar irradiation by increasing HO-1 expression and restoring the physiological expression of ECM proteins [122][123]. Melatonin reduces oxidative stress, not only as a direct ROS/RNS scavenger, but also indirectly via stimulation of antioxidant enzymes and inhibition of pro-oxidant enzymes [118][124]. Indeed, melatonin can upregulate expression of antioxidant genes [55][120][121][125]. Melatonin and its metabolites could also protect DNA from oxidative damages and reduce the levels of CPD's or pyrimidine photoproducts (6-4PP) [120][126][127]. Melatonin, as an endogenous regulator, similarly to vitamin D3, stimulates phosphorylation of p53 at Ser-15 and enhances nucleotide excision repair (NER), thus preventing accumulation of damaged DNA and promoting antitumor activity [112][121][128].

Apart from its anti-oxidative properties, melatonin also preserves mitochondrial function. As we previously proposed, photoprotective functions of melatonin and its metabolites are directly or indirectly dependent on mitochondria, which appear to be a central hub of melatonin metabolism in skin cells [56]. Melatonin protects mitochondria not only directly, by ROS scavenging but also via maintenance of mitochondrial membrane potential and mitochondrial homeostasis in UV-exposed keratinocytes [56][129]. Additionally, melatonin and its metabolites ameliorate UVR-induced mitochondrial oxidative stress in human MNT-1 melanoma cells [130]. These data support the development of novel mitochondria-targeted antioxidants based on melatonin.

Furthermore, the lightening effects of melatonin and some of its metabolites are due to inhibition of proliferation and tyrosinase activity in epidermal melanocytes [110]. Since melatonin and its metabolites over the years have proved their cytoprotective and antiaging properties, topical application of exogenous melatonin and/or metabolites would be a useful strategy against skin aging [131][132].

To enhance the protective effects and prevent wrinkle formation during photoaging, sunscreens and antioxidants (topical and systemic including vitamin C) often are combined with retinoids. The use of retinoids can promote collagen production [70]. Retinoids, especially retinoic acids (RAs) enhance the steroidogenic potential in many classical and non-classical steroidogenic tissues, which decrease due to hormonal imbalance in aging [7][29][133]. Local regulation of steroidogenic activity in keratinocytes of the epidermis is important for skin physiology and

homeostasis. RAs improve wrinkled appearance, post-inflammatory hyperpigmentation and inhibit differentiation of keratinocytes in both mice and humans [\[30\]](#), but they often lead to irritation.

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