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Melatonin: A Cutaneous Perspective on Its Production, Metabolism, and Functions

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Abstract

Melatonin, an evolutionarily ancient derivative of serotonin with hormonal properties, is the main neuroendocrine secretory product of the pineal gland. Although melatonin is best known to regulate circadian rhythmicity and lower vertebrate skin pigmentation, the full spectrum of functional activities of this free radical-scavenging molecule, which also induces/promotes complex antioxidative and DNA repair systems, includes immunomodulatory, thermoregulatory, and antitumor properties. Because this plethora of functional melatonin properties still awaits to be fully appreciated by dermatologists, the current review synthesizes the main features that render melatonin a promising candidate for the management of several dermatoses associated with substantial oxidative damage. We also review why promises to be useful in skin cancer prevention, skin photo- and radioprotection, and as an inducer of repair mechanisms that facilitate the recovery of human skin from environmental damage. The fact that human skin and hair follicles not only express functional melatonin receptors but also engage in substantial, extrapineal melatonin synthesis further encourages one to systematically explore how the skin's melatonin system can be therapeutically targeted in future clinical dermatology and enrolled for preventive medicine strategies.

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The paper is dedicated in gratitude to the memory of Aaron B Lerner, who discovered melatonin and initially defined its activity in pigment cells.

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CONFLICT OF INTEREST

The authors state no conflict of interest.

SUPPLEMENTARY MATERIAL

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MELATONIN: A JOURNEY THROUGH TIME

The methoxyindole, melatonin (*N*-acetyl-5-methoxytryptamine), is produced by at least three clades of bacteria, all clades of eucarya including dinoflagellates, unicellular and multicellular fungi, at least 120 plant species, and numerous animal species including simple and complex vertebrates and invertebrates (Back et al., 2016; Hardeland, 2016; Hardeland et al., 1995; Pöggeler et al., 1991; Tan et al., 2013, 2014).

The presence of melatonin in Alphaproteobacteria and Cyanobacteria indicates an early appearance of this multifunctional serotonin derivative in the evolution of life (Tan et al., 2012, 2013). The discovery of antioxidative properties of melatonin (Hardeland, 2005, 2017; Hardeland et al., 2011; Reiter, 1998; Tan et al., 2002) is consistent with an ancient role of this molecule in contributing to survival under high oxygen levels or exposure to UVR. Because of melatonin production in mitochondria (Reiter et al., 2017b; Suofu et al., 2017; Tan et al., 2013), scavenging of free oxygen radicals has likely been a primary role of melatonin in evolution (Hardeland et al., 1995) originating around 2.5–3 billion years ago (Reiter et al., 2017; Tan et al., 2015).

In all organisms, melatonin is formed from tryptophan via serotonin, with taxon-specific variations in the sequence of steps and intermediates (Back et al., 2016; Hardeland, 2015, 2016; Tan et al., 2012, 2014, 2015, 2016) (Supplementary Text S1 online).

In vertebrates, melatonin is mainly perceived as the hormone of the pineal gland (Lerner et al., 1958 Reiter, 1991). The mammalian pineal gland represents the major source of melatonin in the blood, and in the cerebrospinal fluid of the third ventricle of the brain, where it contributes to the regulation of the circadian system (Reiter et al., 2014). Melatonin is also synthesized in numerous extrapineal sites such as brain, Harderian gland, retina, lens, cochlea, immune system, lungs, gastrointestinal tract, liver, kidney, thyroid, pancreas, thymus, spleen, carotid body, reproductive tract, endothelial cells, and skin (Acuña-Castroviejo et al., 2014; Hardeland et al., 2011; Slominski et al., 2008 Vanegas et al., 2012). Melatonin levels are regulated by its rapid metabolism in the liver or peripheral organs including skin (Slominski et al., 2017b).

Since its origin in early unicells, melatonin, while protecting against oxidative stress, has acquired numerous functions that are taxon, species, and tissue specific. In vertebrates, these functions are manifold and complex, with melatonin acting as a pleiotropic regulator of numerous parameters that orchestrate complex cell and tissue responses, both directly and indirectly (via the circadian system) (Hardeland et al., 2011; Tan et al., 2015). A full record of these functions is summarized elsewhere (Hardeland et al., 2011; Pandi-Perumal et al., 2006; Tan et al., 2015).

MELATONIN IN THE SKIN

Production and metabolism

Normal and pathological skin not only expresses enzymatic elements of the pathway but can also produce serotonin, *N*-acetylserotonin, and melatonin with its metabolites (Kim et al.,

2013, 2015a, 2015b; Kobayashi et al., 2005; Nordlind et al., 2008; Schallreuter et al., 2012; Semak et al., 2004; Slominski et al., 1996, 2002a, 2002b, 2002c, 2003a, 2005c, 2008) (Supplementary Figure S1 online). Skin can also synthesize/recycle the (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin, a cofactor for tryptophan hydroxylase (TPH; Grando et al., 2006; Schallreuter et al., 1997, 1998). Hydroxytryptophan can also be generated in the skin nonenzymatically through H_2O_2 and UVA-induced free-radical-mediated oxidation of L-tryptophan (Schallreuter et al., 2008). In addition to widespread *TPH1* gene expression in skin cells (Slominski et al., 2002b, 2003a, 2005c), we also detected *TPH2* in melanocytes, dermal fibroblasts (Slominski et al., 2014b), and retinal pigment epithelium (Zmijewski et al., 2009). Skin can also express alternatively spliced forms of the melatonin-synthesizing pathway: TPH, arylalkylamine *N*-acetyltransferase, and *N*-acetylserotonin-*O*-methyltransferase (Slominski et al., 2002b). Cutaneous *N*-acetylserotonin is produced by both arylalkylamine *N*-acetyltransferase and arylamine *N*-acetyltransferase (Semak et al., 2004; Slominski et al., 2002a, 2003b).

Melatonin in skin cells is rapidly metabolized through indolic, kynuric, and P450-dependent pathways or via nonenzymatic processes induced by UVR or free radicals (Fischer et al., 2006a; Kim et al., 2013; Slominski et al., 1996, 2017b) (Supplementary Figure S1).

Although immunocytochemistry identified *N*-acetylserotonin and melatonin antigens in epidermal and follicular keratinocytes and melanocytes, adnexal structures, fibroblasts, endothelial cells, and mast cells (Kobayashi et al., 2005; Slominski et al., 2005c, 2008), only recently mass spectrometry quantified melatonin and its metabolites in human epidermis (Kim et al., 2015a, 2015b). Epidermal melatonin production depends on race, gender, and age with the highest melatonin levels in African Americans. Among metabolites, 6-hydroxymelatonin showed the highest levels followed by 5-methoxytryptamine, N^1-acetyl-N^2-formyl-5-methoxykynuramine (AFMK), and N^1-acetyl-5-methoxykynuramine (Kim et al., 2015a, 2015b). Levels of AFMK and N^1-acetyl-5-methoxykynuramine were the highest in African Americans, and no racial difference was seen for 6-hydroxymelatonin and 5-methoxytryptamine. However, skin pathology-related changes in the epidermal content of melatonin and its metabolites remain to be systematically explored to dissect the relationship between their endogenous production and metabolic consumption and defined skin disorders.

Mechanism of action

The potential intracellular targets for melatonin action are shown in Figure 1. The receptor-dependent regulatory functions of melatonin are mediated through interactions with G protein-coupled melatonin type 1 and 2 receptors (MT1 and MT2) (Cecon et al., 2017; Slominski et al., 2012). The latter predominantly work by inhibiting production of second messengers (cAMP, cGMP), thereby modifying signaling pathways downstream of protein kinases A and C, and cAMP response element-binding protein (Dubocovich et al., 2010; Slominski et al., 2012) and by activating MAP kinases (discussed in Hardeland, 2009). MT2 shows a 60% homology in structure to MT1 (Reppert et al., 1996). MT1 and MT2 homodimerize as well as heterodimerize (Jockers et al., 2008), which can affect the pharmacological properties of the receptors (Jockers et al., 2008; Legros et al., 2014). In

addition, their activity is modulated by C-terminal phosphorylation, and, in the case of MT1, by stabilization via the scaffolding protein MUPP1 and inhibition by heterodimerization with GPR50 (Hardeland, 2009).

MT1 and MT2 receptors have been detected in mammalian skin (Fischer et al., 2008a; Kobayashi et al., 2005; Singh and Jadhav, 2014; Slominski et al., 1994, 2005c, 2008). Human skin predominantly transcribes the *MT1* gene, with *MT2* showing restricted or conditional expression (Slominski et al., 2003c, 2005a). Gene expression and production of alternatively spliced or aberrant forms of MT receptors is modulated by UVB and skin pathology (Slominski et al., 2003c, 2005a). In contrast, murine skin showed exclusive expression of the *MT2* gene (Kobayashi et al., 2005; Slominski et al., 2004a). By immunocytochemistry, MT1 was detected in the differentiating layers of the epidermis, outer and inner root sheaths of the hair follicle (HF), eccrine glands, and blood vessels, whereas MT2 was detected in inner root sheath (IRS), eccrine glands, and blood vessels of human skin (Fischer et al., 2008a; Slominski et al., 2005a, 2005c).

It remains to be clarified whether there is also a nuclear receptor for melatonin, because the originally proposed nuclear melatonin receptor candidate, RORα, which is expressed in skin and HFs (Brozyna et al., 2016; Kobayashi et al., 2005; Slominski et al., 2005a, 2014a), has turned out to be a receptor for sterols and secosteroids, but not for melatonin (Slominski et al., 2014a, 2016c, 2017a).

Melatonin and its metabolites act as free radical scavengers and protectors against oxidative stress (Fernández et al., 2015; Fischer et al., 2006c; Galano et al., 2013; Hardeland, 2017; Hardeland et al., 2011). Melatonin and its precursor *N*-acetylserotonin bind to several regulatory proteins including quinone reductase 2 (Jockers et al., 2008; Nosjean et al., 2000). Quinone reductase 2 protects cells against oxidative stress (Boutin, 2016; Hardeland, 2009), against dimethylbenz(a)anthracene-induced skin cancer (Shen et al., 2010), and is required for tumor necrosis factor-α-induced apoptosis in keratinocytes (Ahn et al., 2007). The capability of melatonin binding to this enzyme (see Kleszczynski et al., 2016) requires additional studies.

Calmodulin is another melatonin-binding protein, which may gain physiologically relevant affinity after Ca^{2+} binding and interaction with calmodulin-controlled enzymes, such as calmodulin kinase II and calcineurin, which regulate intracellular calcium homeostasis (Fernández et al., 2015; Fukunaga et al., 2002; Hardeland et al., 2009; León et al., 2000; Lu et al., 2015; Romero et al., 1998). These observations may partially explain the roles of melatonin in the endoplasmic reticulum stress response, regulation of apoptosis and autophagy, and mitochondrial homeostasis (Fernández et al., 2015). Melatonin also regulates mitochondrial functions that affect cellular homeostasis (Acuña Castroviejo et al., 2011; Semak et al., 2005).

FUNCTIONS OF MELATONIN IN THE SKIN

Figure 2 summarizes melatonin effects on the skin, which depend on the route of delivery.

Photoprotection

The ancient functions of melatonin and its metabolites as antioxidants or inducers of responses against oxidative stress or as protectors of genomic integrity are efficiently utilized in the human skin, an organ exposed to different stressors including solar radiation (Fischer et al., 2008b; Slominski et al., 2012, 2014b). Because protective effects of melatonin against UVR were extensively discussed in Fischer et al. (2008b), Kleszczynski and Fischer (2012), Ndiaye et al. (2014), and Slominski et al. (2014b, 2014c), we will focus on the most important and novel aspects of melatonin radioprotection.

Melatonin and AFMK protect human epidermal keratinocytes both in cell and organ culture against UVB (Fischer et al., 2006a, 2006b, 2008b, 2008c, 2013; Kleszczynski et al., 2011, 2013, 2015, 2016). In addition to melatonin, *N*-acetylserotonin, 5-methoxytryptamine, 6-hydroxymelatonin, AFMK, and N^1-acetyl-5-methoxykynuramine protect against or reverse UVB-induced damage in keratinocytes and melanocytes (Janjetovic et al., 2014, 2017). Similarly, melatonin protects dermal fibroblasts against UVA and UVB (Izykowska et al., 2009; Lee et al., 2003; Rezzani et al., 2014; Ryoo et al., 2001).

Although the mechanisms underlying these radioprotective and antioxidative activities are not fully understood yet (Fischer et al., 2006a; Slominski et al., 2005c, 2014b), recent studies implicate the involvement of nuclear erythroid 2-related factor 2 (Janjetovic et al., 2017; Kleszczynski et al., 2016) and sirtuin 1 (Sirt1) (Lee et al., 2016; Ranieri et al., 2015), major regulators of human skin and HF oxidative stress responses, and skin aging (Haslam et al., 2017; Jadkauskaite et al., 2017; Vidali et al., 2016). Clinically, topically applied melatonin can indeed attenuate skin erythema in healthy human subjects exposed to either artificial UVR (Bangha et al., 1996, 1997; Fischer et al., 1999) or natural sunlight (Scheuer, 2017; Scheuer et al., 2016a), thus demonstrating melatonin's clinical potential as a protector against photodamage.

Anticancer activity

The potent anticancer activities of melatonin through a direct action or regulation of circadian rhythms have been discussed in depth elsewhere (Ma et al., 2016; Reiter et al., 2017; Rondanelli et al., 2013; Su et al., 2017). In vitro and in vivo antimelanoma effects of melatonin are established in rodent models (Kadekaro et al., 2004; Narita and Kudo, 1985; Otalora et al., 2008; Slominski and Pruski, 1993; Stanberry et al., 1983). Melatonin and its metabolites also inhibit the growth of cultured human melanomas (Cabrera et al., 2010; Fischer et al., 2006c; Roberts et al., 2000; Souza et al., 2003; Yi et al., 2014; Ying et al., 1993). This raises the question whether topically applied melatonin and its metabolites may be used as adjuvants in difficult-to-resect lentigo maligna or mucosal melanomas.

Clinical trials with high doses of melatonin in late stage of metastatic melanoma suggested its beneficial effect through either reduction of side effects of chemotherapy/chemoimmunotherapy or by enhancing their efficacy (Gonzalez et al., 1991; Lissoni et al., 1997, 2002). Also, an improvement of disease-free survival was observed in patients treated with melatonin after lymph node dissection (Lissoni et al., 1996). Therefore, given its low cost, very favorable toxicological profile, and expected low or absent adverse effects,

systematic clinical testing of melatonin and/or its metabolites as adjuvants in melanoma therapy is both warranted and long overdue.

Melatonin also attenuated benzo[a]pyrene-induced cutaneous sarcomas (Vesnushkin et al., 2006), squamous cell carcinomas (Deriabina et al., 2010), and papillomas (Kumar and Das, 2000) in mice. Patients with basal cell and squamous cell carcinomas had lower urinary indicators of systemic melatonin production in comparison to controls (Ghaderi et al., 2014). Together with its radioprotective function, these additional observations identify melatonin as a promising natural product for clinical use in skin cancer prevention and oncological therapy, which awaits systematic clinical testing.

Epidermal barrier function and wound healing

Exogenously applied melatonin may enhance the skin barrier (Kim et al., 2013). Specifically, melatonin and AFMK in human skin organ culture stimulated expression of involucrin and keratin-10 and keratin-14. It also increased proliferative activity of keratinocytes in ex vivo skin explants (Kim et al., 2013), consistent with earlier observations on murine skin (Slominski et al., 1994). Melatonin can also promote skin wound healing (Lee et al., 2014; Ozler et al., 2010; Pugazhenthi et al., 2008; Romic et al., 2016; Song et al., 2016; Soybir et al., 2003), and can improve the antimicrobial action of wound dressing (Romic et al., 2016). Of note, a novel melatonin-mitochondria axis has been proposed recently as an important regulator of epidermal homeostasis where melatonin and its metabolites coordinate the mitochondrial regulation of epidermal cell destiny by impacting on the decision between cell survival, entry into terminal differentiation as a part of epidermal barrier formation, or to death by apoptosis to evade malignant transformation (Slominski et al., 2017c).

In view of melatonin’s reactive oxygen species-scavenging functions on the one hand, and the recently appreciated physiological key role of a tightly controlled burst of reactive oxygen species production in tissue repair and regeneration on the other (Kimmel et al., 2016; Love et al., 2013), one of the functions of the cutaneous melatonin system (Slominski et al., 2008, 2017c) may also be to control and fine-tune reactive oxygen species availability during wound healing. Thus, preclinical studies on the beneficial role of melatonin and its metabolites on epidermal barrier formation and wound healing are warranted.

Pigmentation

Lightening effects of melatonin on the skin of lower vertebrates and inhibition of pigmentation in some furry animals are well appreciated (reviewed in Slominski et al., 2004b, 2005c). Seasonal changes in hair pigmentation have been attributed in part to melatonin (reviewed in Fischer et al., 2008a; Slominski et al., 2005b). Attenuation of melanogenesis was demonstrated in cultured rodent melanomas (Slominski and Pruski, 1993; Valverde et al., 1995) and in organ-cultured murine skin (Slominski et al., 1994).

In humans, melatonin and some metabolites showed moderate inhibition of tyrosinase and of proliferation of cultured epidermal melanocytes (Kim et al., 2015b). Hardman et al. (2015) have shown that the cutaneous circadian clock elements regulate melanogenesis and melanocyte activities in human epidermis and HFs. Thus, although there are conflicting

results on melatonin functions in human hair and skin pigmentation (McElhinney et al., 1994; Slominski et al., 2004b, 2005c), locally produced melatonin may play a role in the regulation of melanocytic activities via its impact on the peripheral clock. Thus, testing of topically applied melatonin during defined circadian windows as an external modulator of intracutaneous clock activity is warranted (Slominski et al., 2015).

Finally, in light of the autodestruction and oxidative stress theories of vitiligo pathogenesis (Lerner, 1971; Schallreuter et al., 2008), melatonin and serotonin might play a protective role in vitiligo pathogenesis (see viewpoint 4 in Schallreuter et al., 2008). This is further supported by low expression of TPH1 in vitiligo (Schallreuter et al., 2012). Thus, topical supplementation of melatonin and its precursors may be beneficial by ameliorating the oxidative environment of vitiligo skin.

Hair follicle

Melatonin can regulate hair growth directly or indirectly (e.g., via modulating the prolactin serum level) in several nonhuman species (Fischer et al., 2008a; Slominski et al., 2008), and the MT2 expression levels of murine HFs change during HF cycling (Kobayashi et al. 2005). Human scalp HFs also synthesize melatonin, and this intrafollicular melatonin synthesis can be stimulated by noradrenaline, just as in the pineal gland (Kobayashi et al. 2005). Moreover, melatonin may modulate human HF responses to estrogens, because it downregulates intrafollicular estrogen receptor expression (Kobayashi et al. 2005). Studies on human volunteers have raised the possibility that topically applied melatonin may inhibit androgenetic alopecia in women (Fischer et al., 2004, 2012).

Given that melatonin stimulates nuclear erythroid 2-related factor 2 (Janjetovic et al., 2017; Kleszczynski et al., 2016) whereas nuclear erythroid 2-related factor 2 activation protects human HFs against oxidative stress-induced hair growth inhibition (Haslam et al., 2017), it deserves further exploration whether melatonin can protect human hair growth via nuclear erythroid 2-related factor 2 induction. That melatonin renders human HFs ex vivo less susceptible to chemotherapy-induced damage (Kobayashi et al., 2005) may be related in part to this putative protective mechanism. Furthermore, involvement of circadian clock proteins in the control of human HF cycling (Al-Nuaimi et al., 2014) and of both epidermal and HF pigmentation (Hardman et al., 2015) raises the question whether melatonin can impact on the control of human hair growth and pigmentation via modulating peripheral clock activity in the skin, just as it does centrally.

Inflammatory dermatoses

The role of melatonin in immunodermatology remains insufficiently defined because both immunostimulatory and anti-inflammatory actions of melatonin have been reported (Carrillo-Vico et al., 2013; Jahanban-Esfahlan et al., 2017). Yet, key innate skin immunocytes such as mast cells express melatonin receptors (Theoharides, 2017) and melatonin plays an important role in T-cell fate determination, T-cell-based immune pathologies (Ren et al., 2017), and macrophage function (Kadena et al., 2017; Yi and Kim, 2017).

Despite a shortage of information on the role of melatonin in inflammatory skin disorders, beneficial effects of melatonin have been suggested in atopic dermatitis (Calvo and Maldonado, 2016; Marseglia et al., 2014, 2015; Park et al., 2017) and seborrheic dermatitis (Fischer et al., 2012), and disturbances in serum melatonin levels were reported in patients with psoriasis (Kartha et al., 2014; Mozzanica et al., 1988). Thus, studies that define the role of melatonin in chronic inflammatory skin diseases are warranted, and may lead to a discovery of beneficial effects similar to those recently described for multiple sclerosis (Farez et al., 2015).

Thermoregulation

Melatonin directly or via its circadian effects influences core body and skin temperature (Atkinson et al., 2005; Cuesta et al., 2017; Filadelfi and Castrucci, 1996; Kräuchi et al., 1997; van den Heuvel et al., 1999). It can modify the cutaneous vasodilator response to heat (Aoki et al., 2006) and is involved in the fine-tuning of vascular tone and modifies cutaneous vasoconstrictor response to whole body skin cooling (Aoki et al., 2008; Kräuchi et al., 2006). However, it remains unknown whether melatonin also plays a role in sweat gland physiology.

CONCLUSIONS AND TRANSLATIONAL PERSPECTIVES

That mammalian skin and HFs not only are prominent melatonin targets but also produce and rapidly metabolize this multifunctional methoxyindole to biologically active metabolites is of considerable dermatological interest and potentially of great clinical importance for future dermatological therapy. Here, we have delineated why sufficient levels of locally produced melatonin and its metabolites are required for both optimal skin homeostasis, thus preventing skin pathology, and optimal responses to environmental stressors including UVR. Therefore, physiological concentration of melatonin will depend on the biological context. In fact, the serum melatonin level may be largely irrelevant, because skin produces a much larger amount of melatonin for its own use than can be detected in serum (Kim et al., 2015b; Slominski et al., 2008), similar to the gastrointestinal system that contains several hundred times more melatonin than the pineal gland itself (Bubenik, 2002).

Although we have reviewed here how melatonin and its metabolites can impact on multiple aspects of human skin physiology, challenging open questions include how exactly these agents affect human skin pigmentation, hair growth, and the development of melanoma and nonmelanoma skin cancers mechanistically and under clinically relevant circumstances. This still needs to be clarified definitively in appropriately designed clinical studies. The translational perspectives that emanate from melatonin’s unique properties in multiple oxidative damage control and DNA repair systems and its immunomodulatory properties render melatonin an especially attractive candidate agent in the future management of dermatoses associated with substantial oxidative, photo-, and radiation-induced damage. Melatonin also promises to be useful in skin cancer prevention. In addition, in view of melatonin's capability to induce multiple damage reparative mechanisms in skin, the potential anti-skin aging properties of melatonin deserve systemic study.

Given that melatonin is essentially nontoxic, readily available over the counter in different formulations, and that many of its metabolites meet the definition of natural products, their topical and transepidermal delivery is a promising area for full exploration in future dermatotherapy and preventive skin medicine.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AFMK	N^1-acetyl-N^2-formyl-5-methoxykynuramine
HF	hair follicle
MT1 and 2	melatonin type 1 and 2 receptors
TPH1 and 2	tryptophan hydroxylase 1 and 2

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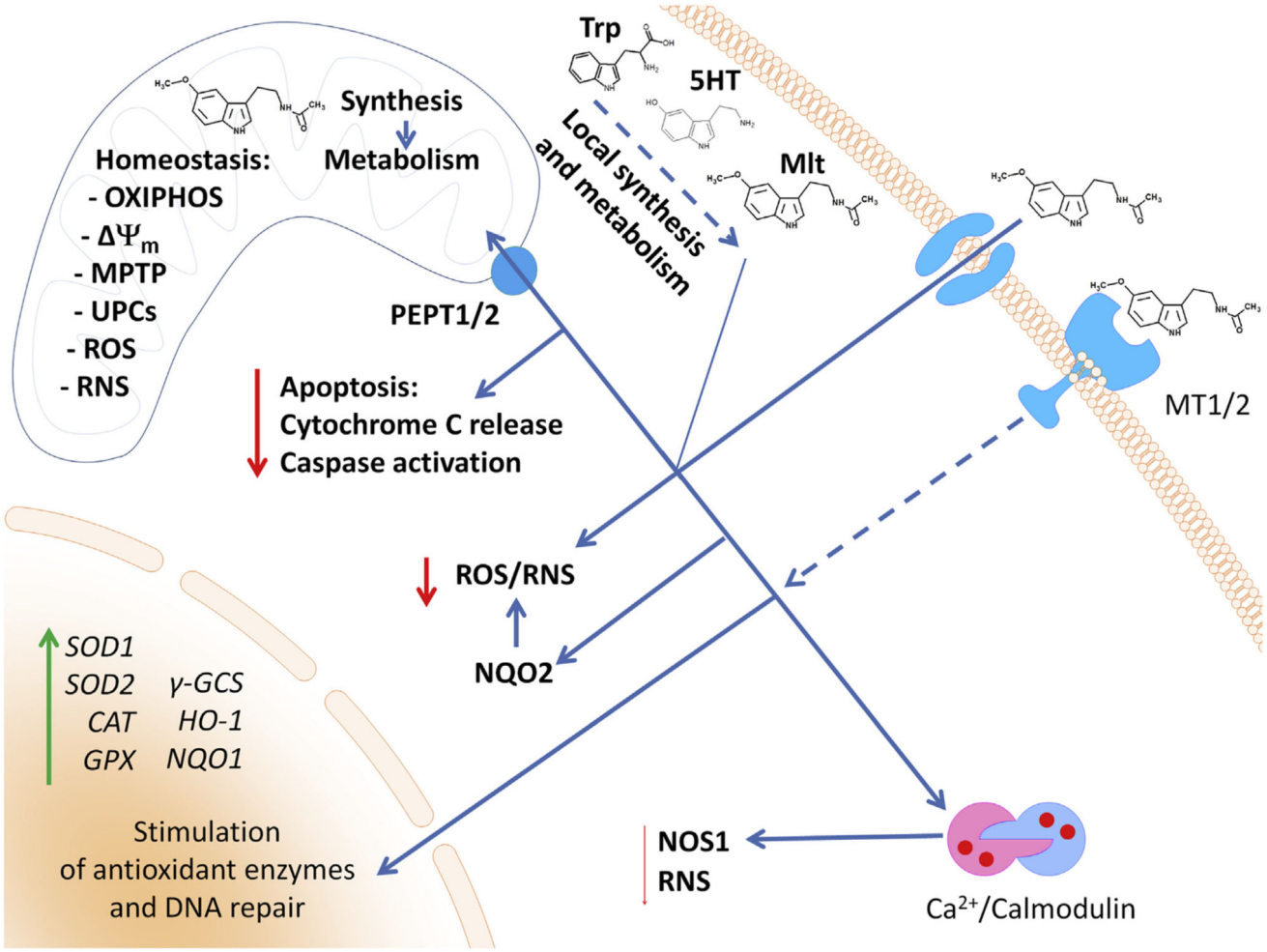

Figure 1. Targets for melatonin action in skin cells

Melatonin, depending on the concentration, binds to membrane-bound receptor MT1 or MT2. Subsequent activation of signal transduction cascades stimulates the expression of antioxidative enzymes and DNA repair. Melatonin might also be transported to cytoplasm; however, the detailed mechanism is not fully understood. In a cell, melatonin at concentrations higher than 1 nM interacts with the calcium/calmodulin complex, which inhibits NOS1-mediated generation of RNS. On the other hand, melatonin can also interact with NQO2 (previously described as MT3) with potential inhibition of ROS/RNS levels. Recently, peptide transporter PEPT1/2 was found to be responsible for melatonin transport to mitochondria (Huo et al., 2017). Melatonin improves mitochondrial membrane potential ($\Delta\psi_m$) by inhibition of the mitochondrial permeability transition pore (MPTP) and stimulation of uncoupling proteins (UCPs). This results in an elevated production of ATP by oxidative phosphorylation (OXIPHOS). These effects will also depend on its local synthesis (tryptophan (Trp) → serotonin (5TH) → melatonin (Mlt)) and metabolism. NQO2, quinone reductase 2; ROS, reactive oxygen species, RNS, reactive nitrogen species.

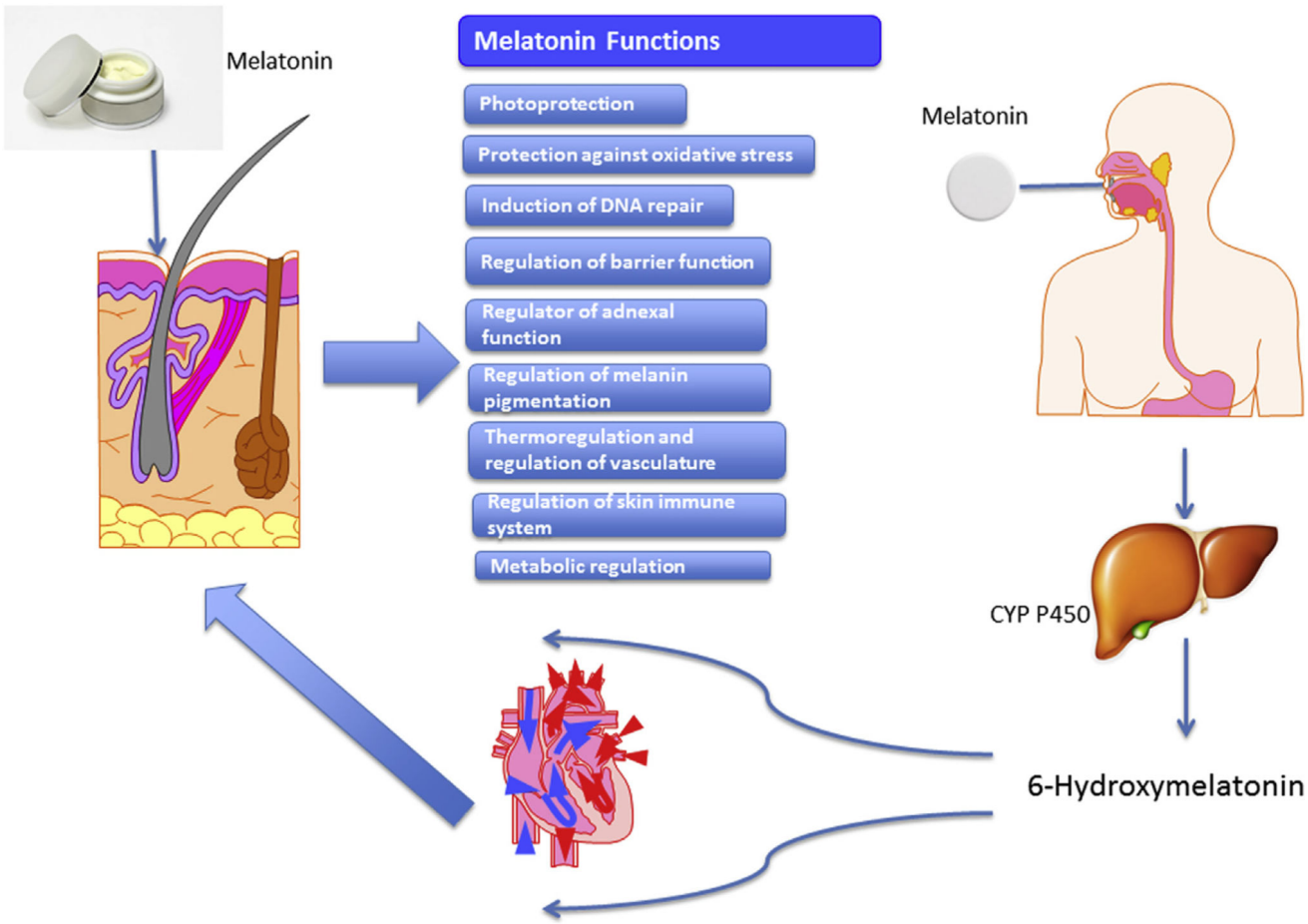

Figure 2. Topically or orally administered melatonin affects different skin functions

To compensate inadequate intracutaneous levels of melatonin secondary to environmentally induced degradation or suboptimal local production or transport from the pineal gland, melatonin can be delivered to the skin via different routes. Orally ingested melatonin is rapidly metabolized in the liver by CYP450 into 6-hydroxymelatonin while sublingual (transmucosal) melatonin administration can bypass liver metabolism. Transdermal application of melatonin appears to be optimal for local application due to slow absorption, deposition in the skin, lack of identifiable site effects, and availability of different formulations (Flo et al., 2016, 2017; Milan et al., 2017; Romic et al., 2016; Scheuer et al., 2016b; Zetner et al., 2016). Because there is a cutaneous melatonin metabolism with metabolites sharing similar activities as melatonin (Slominski et al., 2017b), the effects summarized in the central column may also be secondary to the action of its metabolites. Of note, 6-hydroxymelatonin, 4-hydroxymelatonin, 2-hydroxymelatonin, AFMK, or AMK being produced by different species, in addition to the human body, may fulfill the definition of natural products for topical applications to improve healthy skin status. Importantly, the functional effects depicted here may also be exerted by endogenous melatonin synthesized in the skin and hair follicles (see main text). AFMK, N^1-acetyl-N^2-formyl-5-methoxykynuramine; AMK, N^1-acetyl-5-methoxykynuramine; CYP, cytochrome P450.