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Sensing the environment: Regulation of local and global homeostasis by the skin neuroendocrine system

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1. INTRODUCTION

1.1. General overview

The strategic location of the skin as the barrier between the environment and internal milieu determines its critical function in the preservation of body homeostasis, and ultimately organism survival (Slominski, 2005, Slominski and Wortsman, 2000, Slominski et al., 2000c, Zmijewski and Slominski, 2011). It also exposes skin to numerous pathological agents, processes, and events. Thus, the capability to locally recognize, discriminate and integrate various signals within a highly heterogeneous environment, and to immediately launch appropriate responses, is a vital property of skin (Slominski and Wortsman, 2000). These skin functions are integrated into the skin immune, pigmentary, epidermal and adnexal systems, and are in continuous communication with the systemic immune, neural and endocrine systems (Arck et al., 2006, Slominski, 2009c, Slominski et al., 2004c, Slominski and Wortsman, 2000, Slominski et al., 2007a, Stenn and Paus, 2001).

These fundamental functions results from the location of the skin, which is the largest body's organ, at the interphase between external and internal environment, requiring development of efficient sensory and effector capabilities to differentially react to changes in external environment. They are represented by inducible production of biologically active compounds (hormones, neurohormones and neurotransmitters) that act both locally and at the systemic levels (Fig. 1).

The skin being continuously exposed to many external biological or environmental factors (acute transfers of solar, thermal or chemical energy), had to evolve optimal mechanism(s) to protect, restore or maintain local and global homeostasis in relation to hostile environment (Slominski et al., 1993b, Slominski and Pawelek, 1998, Slominski and Wortsman, 2000, Slominski et al., 2000c). We have proposed that precise coordination and

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execution of these responses are mediated by a cutaneous neuroendocrine system, which also is able to reset the body homeostatic adaptation mechanisms (Slominski and Wortsman, 2000). Superimposed on this is the impact of psychological stress on skin physiology and pathology, placed in the context of the bidirectional brain-skin communication (Arck et al., 2006, Slominski, 2005a, Slominski et al., 2008b). To summarize, in reaction to changing external and also internal environment, the skin can generate signals to produce rapid (neural) or slow (humoral or immune) responses at the local and systemic levels (Fig. 1).

Coordination between these local and systemic responses is mediated by the skin neuroendocrine system (Slominski and Wortsman, 2000a), which employs local equivalents of the hypothalamo-pituitary-adrenal axis (HPA) (Slominski et al., 2007a), hypothalamo-pituitary-thyroid (HPT) axis (Pisarchik and Slominski, 2002, van Beek et al., 2008), catecholaminergic (Schallreuter et al., 1997), serotoninergic, melatoninergic (Slominski et al., 2008a, Slominski et al., 2005c), cholinergic (Grando, 2006, Grando et al., 2006), steroidogenic (Slominski et al., 2008b) and secosteroidogenic (Bikle, 2010, Holick, 2003, Slominski et al., 2010) systems (Fig. 2). Given their common embryonic origins, it is not surprising that skin shares numerous mediators with the CNS and endocrine system. Recent research has revealed that skin also harbors a complex opioidogenic (Grando et al., 1995, Slominski et al., 2011c) and canabinnoidogenic (Biro et al., 2009) systems, which role in the maintenance of cutaneous homeostasis is currently being intensively explored.

In this monograph we will discuss the role of various components of the skin neuroendocrine system in sensing the environment with subsequent regulation of local and global homeostasis with a main focus on the algorithms of classical neuroendocrine axes.

1.2. An overview of histology and anatomy

Since histology and anatomy of the skin has been extensively reviewed in three major dermatology and dermatopathology texbooks (Bolognia et a., 2008, Fitzpatrick et a., 1993, Weedon, 2010), below we provide only a short overview. The most external layer of the skin, the epidermis, is derived from the ectoderm, and is characterized by constant renewal. The main constituents of the epidermis, keratinocytes, are either self-replicating in the basal layer (about 50% of basal layer keratinocytes are in this state) or are differentiating towards the surface (another 50%). The whole process of differentiation lasts about 31 days. The keratinocytes of succeeding layers (spinous and granular) gradually flatten to form a solid cornified layer that is subsequently shed (this takes another 14 days on average). The intermediate filaments, cytokeratins, are the most important structural elements of the keratinocyte. In the epidermis, cytokeratins 5 and 14 are main cytokeratins in basal keratinocytes and cytokeratins 1 and 10 in differentiating ones. The cornified layer is formed by various cross-linked proteins and lipids. Apart from keratinocytes there are other cells in the epidermis whose function is more regulatory than structural. Examples are melanocytes, derived from neural crest, which reside in the basal layer. Their density varies in different parts of the body from 1 in 4 to 10 basal keratinocytes. Melanin, protective pigment produced by these cells, is transferred from melanocytes through their processes to approximately neighboring 36 keratinocytes (to form epidermal-melanin unit) by the process of apocopation. Melanin not only absorbs UV irradiation but also serves as a scavenger of reactive oxygen species and miscellaneous chemical compounds. The Langerhans cells are derived from the bone marrow. They reside at different levels of the epidermis and engulf foreign antigens. They transport them to the lymph nodes and present in the context of MHC antigens to T lymphocytes initiating the adaptive immune response.

The dermis is derived from mesoderm. Its bulk is composed of collagen and elastic fibers and glycosaminoglycans. The main collagen of reticular dermis is collagen type I. Collagen type III is present in the adventitial dermis (papillary and peri-appendageal). Elastic fibers

are arranged in a parallel manner in the superficial dermis including eulanin fibers (made of microfibrils with elastin core) and perpendicular manner in the papillary dermis (oxytalan fibers made of microfibrils only). Collagen gives skin its strength, elastic fibers its elasticity (ability to retract) and glycosaminoglycans its substance. Various inflammatory cells typically reside in the dermis and increase in numbers when need arises. Dermal vasculature forms superficial and deep dermal plexuses that are connected by straight collaterals. Superficial plexus sends papillary loops towards the surface. Of note, the epidermis does not have its own vasculature and is being nourished through exchange of substances provided by the most superficial parts of papillary capillaries. Glomus bodies (Sucquet-Hoyer canals) are important for local thermoregulation.

Skin appendages are of epidermal origin. The hairs cover most of the body. Terminal and vellus hairs differ in their size and function. The hairs undergo cyclic changes of growth (anagen, about 90% of scalp hair, lasts 3–10 years), involution (catagen, 1%, lasts weeks) and rest (telogen, 10%, lasts few months). Of note, different hair on the body, even directly neighboring, are in different phases of the growth cycle. This is a major difference between humans and animals that shed hair cyclically. The sebaceous glands are usually associated with hair and secrete protective lipid substances by a holocrine mechanism. The coiled eccrine glands are located in the subcutis, their straight ducts transverse the dermis and end in coiled fashion in the acrosyringia of the epidermis. The primary sweat is hyper- or isotonic and becomes hypotonic during passage through the excretory ducts. Sweat production is the most important thermoregulatory mechanism in humans. Apocrine glands are distributed only in some areas of the body (axillae, genital, ear, eyelid) and have probably only vestigial function in humans.

Last, but not least, the subcutaneous fat tissue is a third important layer of the skin. Fat lobules forming it are separated by fibrous septae transverse rich in vasculature. The adipose tissue is mostly of white type and has important function in isolation, cushion and energy storage. Often quoted to be body's largest immune/endocrine organ (about 15% of body weight and average surface of about 2 m^2), skin is a source of multiple mediators and cytokines that act not only locally but also systemically. On the other hand, components of skin respond to internal stimuli and mediators preserving body homeostasis and appropriate functioning.

Skin is studied by a variety of methods. The classic histological slides, prepared from formalin-fixed tissue and stained with hematoxylin and eosin paired with various special stains and by immunohistochemical methods, are the tools of both dermatopathologist and researcher. Direct immunofluorescence is a complementary method used for both diagnosis and research. Frozen sections are stained here with antibodies against immunoglobulins, complement and fibrinogen. Different patterns are observed and yield diagnostic information. Popular research tool are the ex vivo skin cell cultures. Both primary (with definite number of cell divisions) and continuous (indefinite number of cell divisions) cell cultures are being used. To better model the conditions present at the skin as tissue, the ex-vivo organ cultures are also used. Plethora of cell and molecular biology methods have been applied for studies of both cell and organ cultures. Some popular examples are Western blot, PCR, confocal microscopy and gene microarrays.

1.3. An overview of skin innervation

The skin extensive neural network represented by somato-sensory and autonomic nerve fibers have been described in details in several reviews and books (Bolognia et al., 2008; Fitzpatrick et al., 1993; Joachim et al., 2007; Roosterman et al., 2006; Siemionow et al., 2011; Slominski and Wortsman, 2000; Weedon, 2010; Yosipovitch, 2010). Therefore, below we provide only a short overview.

In the skin, receptors localized on the primary afferent nerve terminals transduce various sensory stimuli, generated upon changes in temperature, pH, presence or inflammatory mediators, and convey them to the specific areas of the CNS what results in the perception of pain, itching neuroinflammation, as well as somatic responses of other organs and tissues. The perikarya of cutaneous sensory fibers are localized either in the dorsal root ganglia (DRG) or, those innervating the face and upper neck, in the trigeminal ganglion. Both, unmyelinated (C) and myelinated (A) fibers of unipolar sensory cells conduct thresholds at 0.5–2 m/sec and 4–70 m/sec, respectively. The both ortho/antidromic conduction of afferent nerve fibers results in simultaneous signal transduction and release of neurotransmitters (mainly substance P and CGRP) at the same site. The sensory axons make synapses in dorsal spinal cord neurons depending on somatotopic map of the part of the body surface innervated by the relevant spinal segments. The major ascending routes for sensory cutaneous inputs are via the DCN (dorsal column nuclei) or LCN (lateral cervical nucleus). Both of them transmit to the thalamus, which is a coordinator station for sensory imputes receiving and sending neural signals to somatosensory cortex, midbrain and hypothalamus - the headquarters of the autonomic nervous system. The connection between thalamus and hypothalamic paraventricular nuclei constitutes important element joining cutaneous stimuli with centers which control body homeostasis and endocrine system, including HPA axis. Also cutaneous afferent stimuli from face run in the trigeminal root and upon switch in trigeminal nucleus terminate in thalamus (Siemionow et al., 2011).

The cutaneous innervation has traditionally been considered to consist of a plexus of fibers in the reticular layer of dermis and a more superficial plexus in the papillary layer, with the majority of sensory endings located in the subpapillary dermis. Recent advances in immunohistochemistry provided an evidence for the existence of intraepidermal nerve fibers (reviewed in Bolognia et al., 2008; Legat and Wolf, 2009; McArthur et al., 1998; Roosterman et al., 2006; Slominski and Wortsman, 2000; Walter et al., 2011). Intraepidermal nerve terminals associated with Merkel cells, cold receptors and high-threshold mechanoreceptors have been identified in the basal layer of the epidermis. Thin nerve fibers travel through the dermis, extend into epidermis, and terminate with or without branching in all layers of epidermis including stratum corneum. Waller et al., 2011). The density of epidermal nerve fibers changes during aging and in many pathological conditions like diabetes, psoriasis or upon ultraviolet radiation. Therefore, quantification of the epidermal nerve fibers' density was proposed to be a valuable prognostic marker for the evaluation of the disease progress (Fromy et al., 2010; Joachim et al., 2007; Legat and Wolf, 2009; Roosterman et al., 2006; Walter et al., 2011).

In the skin, cutaneous nerve fibers have principally sensory character, with an additional component of autonomic nerve fibers distributed exclusively in dermis. Most of them are found in the mid-dermis and the papillary dermis. The autonomic nerves supply arterioles, glomus bodies, hair erector muscles, and apocrine and eccrine glands. A rich network of autonomic and sensory nerve fibers surrounds especially hair follicles, pilosebaceous units, eccrine and apocrine glands. The sensory and autonomic networks show regional differences according to anatomic location and also have topographical specificity by distributing into well-defined areas called dermatomes. The autonomic nerve fibers in the skin predominantly derive from sympathetic (cholinergic, catecholaminergic, and non-adrenergic/non-cholinergic) and, in the face, rarely parasympathetic (cholinergic) neurons.

In addition to the classic neurotransmitters like acetylcholine, noradrenaline and serotonin, the postganglionic autonomic nerves in the skin predominantly release also neuropeptides (neuropeptide Y, galanin, vasoactive intestinal peptide, β-endorphin) and biologically active substances (nitric oxide, ECS) which act as co-transmitters. These compounds modulate the release and activity of the main neurotransmitters and also directly affect targeted cells.

Neuropeptides released from cutaneous nerves via a paracrine, juxtacrine, or endocrine manner act on target cells which express specific receptors that are appropriately coupled to an intracellular signal transduction pathway or ion channels, which, when activated, may result in the activation of biological responses such as erythema, edema, hyperthermia, and pruritus.

2. BIOGENIC AMINES IN THE SKIN

2. 1. An overview

It has been documented that skin resident cells can produce and further metabolize catecholamines, serotonin and histamine (Fitzpatrick et al.,, 1993, Gillbro et al., 2004, Schallreuter et al., 1995, Slominski et al., 2005c). These biogenic amines not only regulate phenotype of skin cells cultured in vitro but also can affect skin functions and may have systemic effects (Schallreuter et al., 1997, Slominski and Wortsman, 2000, Slominski et al., 2005c). The functional activity of biogenic amines in the skin is mediated through the interactions with specific cell surface receptors (Gillbro et al., 2004, Nordlind et al., 2007, Slominski et al., 2003c), however, non-receptor effects are also considered.

2.2. Catecholamines

2.2.1. Production and metabolism—Non-essential aromatic amino acid L-tyrosine, depending on the cell type and enzymatic context, serves as a direct precursor to catecholamines, tyramine/octopamine (Yen, 2001) and melanin pigment (Slominski et al., 2004c). To serve these diverse functions, L-tyrosine is either delivered through the gastrointestinal tract (GI) or is produced through phenylalanine hydroxylase (PH) mediated hydroxylation of L-phenylalanine (Blau et al., 2010, Schallreuter et al., 2008b). L-tyrosine is hydroxylated to L-dihydroxyphenylalanine (L-DOPA) either by tyrosine hydroxylase (TH) or tyrosinase (Tyr) or decarboxylated to tyramine by L-amino acid decarboxylase (AAD) (Fig. 3). L-DOPA is further decarboxylated to dopamine by AAD with subsequent hydroxylation and methylation reactions to generate norepinephrine or epinephrine, all of them being oxidated by monoamine oxidase (MAO) or methylated by catechol-methyl transferase (COMT) (Fig. 3). L-DOPA and catecholamines can also be oxidized either by tyrosinase or metal cations to form melanin and neuromelanin pigments (Fitzsimons et al., 2002, Lassalle et al., 2003, Park et al., 2009, Slominski et al., 2004c) (Fig. 3).

Human epidermal keratinocytes and melanocytes have the capability to synthesize the catecholamines from L-tyrosine with sequential production of L-DOPA, dopamine, norepinephrine, and epinephrine through the action of classical enzymes listed above with the subsequent inactivation of catecholamines by MAO or COMT (Fig. 4) (Fuziwara et al., 2005, Gillbro et al., 2004, Schallreuter et al., 1995, Schallreuter et al., 1992). Interestingly, acetylation of dopamine to N-acetylDOPA has also been described in the hamster skin (Gaudet et al., 1993). Activity of TH and PH depends on local availability of their essential cofactor/electron donor, i.e. 6R-L-erythro-5, 6, 7, 8-tetrahydrobiopterin (6BH4) as demonstrated for the first time by Schallreuter's group (Schallreuter et al., 1994, Schallreuter et al., 1997). Importantly, Schallreuter and coworkers demonstrated de novo synthesis/recycling/regulation of 6BH4 in both human epidermal keratinocytes and melanocytes as well as in hair follicles (Schallreuter et al., 1998, Schallreuter et al., 1997). Furthermore, AAD activity requires pyridoxal phosphate (PP) as the cofactor, which cutaneous availability is regulated locally (Coburn et al., 2003). Lymphocytes and other immune cells can also represent an additional source of catecholamines: L-DOPA production with its further transformation to epinephrine and norepinephrine has been shown in human lymphocytes (Musso et al., 1997) as well as in Langerhans cells (Falck et al., 2004). An additional cutaneous source of catecholamines is their dermal release from

adrenergic nerve fibers (Fitzpatrick et al.,, 1993). A challenging task in current skin biology is to determine, which skin cells and adnexal structures have similar capability of de novo synthesis of catecholamines and what is the final product in different compartments.

An important alternative source of L-DOPA for cutaneous catecholamines is its production via the tyrosine hydroxylase activity of tyrosinase that, depending on the intracellular environment including acidic pH, may not undergo oxidation but will diffuse or be transported to other cells or systemic circulation (Slominski et al., 2004c, Slominski et al., 2011a). In fact, diffuse 'melanocytic organ' can provide DOPA or its adducts to systemic circulation to either serve as a precursor for further modifications or as a bioregulator (Slominski et al., 1993a, Slominski et al., 2011a, Zmijewski and Slominski, 2009a). A role for tyrosinase-derived L-DOPA is supported by findings that retinal network adaptation to bright light requires tyrosinase-dependent production of DOPA (Page-McCaw et al., 2004). This phenomenon represents the TH-independent pathway of peripheral dopamine synthesis (Eisenhofer et al., 2003) and it can regulate activities of melanocytes and immune cells (Slominski and Paus, 1990, Slominski et al., 1998c). These findings are in agreement with our hypothesis that L-tyrosine and L-DOPA can have hormone- and neurotransmitter-like roles (Slominski and Paus, 1990, Slominski and Paus, 1994, Slominski et al., 2011a), with melanocytes acting as important regulators of catecholamines' availability in the skin (Slominski et al., 1993a).

2.2.2. Bioregulatory role of catecholamines in the skin

2.2.2.1. Dopamine receptors: There are five subtypes of dopamine receptors, and they have been categorized into two families, i.e., D1-like receptors (D1 and D5) and D2-like receptors (D2, D3, and D4) (Watson S, 1994). The D1-like receptor agonists stimulate Gs-dependent intracellular production of cAMP (Missale et al., 1998). The D2-like receptor agonists activate Gi proteins and inhibit intracellular cAMP signaling pathway (Missale et al., 1998, Watson S, 1994). In addition, via Gβγ-subunits, D2-like receptors are capable of inhibiting N- and L-type calcium channels which results in the activation of G protein-regulated inwardly rectifying potassium channels (GIRKs) (Beaulieu and Gainetdinov, 2011). After D2-like receptors were identified in the keratinocytes (Fuziwara et al., 2005) they were found to play a significant role in the maintenance of epidermal barrier homeostasis. Application of D2-like receptor agonists accelerated barrier recovery, whereas D2-like receptor antagonists delayed it. Actual receptor subtypes localize to different parts of the epidermis: D4 is localized in the uppermost part of the epidermis and D2 is localized in the basal layer of the epidermis where it plays a role in the regulation of cell proliferation (Fuziwara et al., 2005). It remains to be tested whether dopamine is also regulating epidermal and follicular pigmentary systems as well as adnexal functions including hair follicle.

Dopamine receptors on lymphocytes exert differential effects. Dopaminergic signaling through D2-like receptors of T lymphocytes showed an immunostimulatory effect (Besser et al., 2005), whereas signaling through D1-like receptors had immunoinhibitory effect (Saha et al., 2001). Dopamine also inhibits proliferation of human lymphocytes and causes apoptosis of peripheral blood mononuclear cells (Bergquist et al., 1997). IL-6 (and other cytokines) stimulates a development of a subtype of T lymphocytes capable of producing IL-17 (and other cytokines), i.e. Th17 lymphocytes. Th17 lymphocytes constitute relatively recently described branch of immune responses (Harrington et al., 2006). Dopamine released by dendritic cells induces IL-6–Th17 axis and up-regulates synovial inflammation (Nakano et al., 2011). The IL-6-Th17 axis plays a role in the pathogenesis of inflammatory diseases including rheumatoid arthritis. It can therefore be deduced that dopamine may also have various differential modulatory roles in the skin immune system.

2.2.2.2. Adrenergic receptors: The adrenergic receptors belong to the classic seven-transmembrane G-protein–coupled receptor (GPCR) family. These receptors respond to catecholamines and can be subdivided into subtypes of α and β families, based on their differential pharmacological responses and protein sequences (Lands et al., 1967). More specifically, these receptors are defined, in part, by their endogenous ligand affinity to β receptors having a higher affinity to epinephrine when compared to norepinephrine, and to α receptors having a higher affinity for norepinephrine. Alpha adrenergic receptors can be further subdivided into α1 and α2, and β receptors can be further subdivided into β1, β2 and β3 subtypes. The α1 (α1a, α1b, and α1d) receptors couple to phospholipase C via Gqα and stimulate the formation of diacylglycerol and inositol trisphosphate (Cotecchia, 2010). The α2 (α2a, α2b and α2c) receptors couple to Giα and inhibit the formation of cAMP whereas β receptors are positively coupled to the formation of cAMP via Gsα (Hein, 2006).

Various receptors of both α and β subfamilies of adrenergic receptors are present on epidermal and dermal cells (Grando et al., 2006, Schallreuter et al., 1995). As expected, α- and β receptors are also expressed in dermal blood vessels. Their activation by catecholamines causes vasoconstriction and decreases vascular permeability (Ding et al., 1995, Harada et al., 1996).

Keratinocytes express mainly β2 receptors and also α1 receptors (Steinkraus et al., 1992, Drummond et al., 1996, Sivamani et al., 2007). Stimulation of β-adrenergic receptors in epidermal keratinocytes results in increased cAMP production, activation of protein kinase C and formation of inositol-1,4,5-trisphosphate, calcium influx and extracellular signal-related kinase (ERK) dephosphorylation through the action of serine/threonine phosphatase PP2A (Chen et al., 2002, Pullar et al., 2001, Schallreuter et al., 1995). Catecholamines stimulate keratinocyte differentiation with increased expression of keratins 1, 10, involucrin and transglutaminase (Mammone et al., 1998, Schallreuter et al., 1995). Moreover, there is a local gradient of receptor expression with the highest level in basal keratinocytes and decreasing level towards the surface of the epidermis (Schallreuter et al., 1995). This indicates a potential stimulatory functional role of catecholamines in the process of keratinocytes' differentiation. Catecholamine-β2 adrenergic system has been implicated in the pathogenesis of atopic dermatitis, psoriasis and vitiligo (Sivamani et al., 2007). Expression of β2 receptors is increased in vitiligo and decreased in psoriasis (Schallreuter et al., 1993, Takahashi et al., 1996). In vitiligo, there is an overproduction of 6-BH4 leading to a dysregulation of catecholamine biosynthesis with increased plasma and epidermal norepinephrine levels. This is associated with high numbers of β2 adrenoceptors in differentiating keratinocytes and with a defective calcium uptake in both keratinocytes and melanocytes (Schallreutter et al., 2008a). In atopic eczema, a point mutation in the beta 2-adrenoceptor gene could alter the structure and function of the receptor, thereby leading to a low density of receptors on both keratinocytes and peripheral blood lymphocytes (Schallreuter et al., 1997). It is also known that catecholamines and β receptors have a role in wound healing although their exact role is far from being clarified (Ghoghawala et al., 2008, Pullar et al., 2008) (see also discussion of fibroblast below). The adrenergic beta-receptors not only affect keratinocytes' proliferation and differentiation but also their immune activities. Activation of β receptors on keratinocytes affects expression of β-defensin 3 (Martin-Ezquerra et al., 2011).

Studies on cultured melanoma cell lines have shown that catecholamines can be an additional factor affecting melanogenesis (Howe et al., 1991). Their role in the function of the pigmentary system has been well described in non-human systems (reviewed by Slominski et al., 2004c). Human melanocytes express α1 and β2 receptors (Gillbro et al., 2004, Hu, 2000, Hu et al., 2000, Scarparo et al., 2000, Schallreuter et al., 1996). Activation of α1 receptors leads to the IP3-DAG signaling (Schallreuter et al., 1996) and β2 receptor

activation leads to cAMP signaling (Gillbro et al., 2004). β2 but not α1 receptor activation induces pigmentation (Gillbro et al., 2004, Schallreuter et al., 1996). The expression of β2 receptors on human melanocytes increases in response to UV irradiation (Yang et al., 2006). UVB irradiation increases epinephrine release by cultured keratinocytes that in turn increases pigmentation in co-cultured melanocytes, which is an example of the interactions between these two cell types (Sivamani et al., 2009).

Adrenergic receptors are expressed also on immune cells of the dermis (Steinkraus et al., 1996). Binding of adrenergic agonists to their receptors on lymphocytes has immunostimulatory effect and affects their homing. On the contrary, stimulation of β receptor usually has immunosuppressive effects but in other model systems can also cause immunostimulation, i.e. increase the number of lymphocytes (Bergmann and Sautner, 2002).

Mouse Langerhans cells express α1, β1 and β2 adrenergic receptors (Seiffert et al., 2002), and it was shown that epinephrine and norepinephrine inhibit the ability of Langerhans cells to present antigens (Seiffert et al., 2002).

Agonists of β2 receptors on mast cells inhibit the release of preformed mediators such as histamine, and also newly synthesized mediators such as prostaglandin D2 from mast cells (Okayama and Church, 1992). They also inhibit release of inflammatory cytokines from mast cells (Bissonnette and Befus, 1997). β receptors are expressed on dermal fibroblasts (Pullar and Isseroff, 2006, Pullar et al., 2008). Ligation of β2 receptors activates epidermal growth factor (EGF) receptor and extracellular signal-regulated kinase (ERK) signaling that in turn stimulates fibroblast migration. Binding of agonists to the β2 receptors can also activate protein A kinase (PKA) what can stimulate cell proliferation (Pullar and Isseroff, 2006), attenuate collagen gel contraction and alter actin cytoskeleton and focal adhesion distribution via PKA-dependent mechanisms (Pullar and Isseroff, 2006). A link between body stress response system that results in the release of epinephrine and activation of intracellular signaling that leads to DNA damage has been shown recently (Hara et al., 2011). Specifically, in mouse and human fibroblasts binding of agonists to the β2 receptors led to Gs-protein-dependent activation of protein kinase A, followed by the recruitment of beta-arrestins. Then, β-arrestin 1 facilitated AKT-mediated activation of MDM2 and also promoted MDM2 protein binding to, and degradation of p53 protein, by acting as a molecular scaffold. The degradation of p53 resulted in the lack of protection and DNA damage [Hara et al., 2011).

2.2.2.3. Non-receptor mediated effects of catecholamines: In the skin there are several potential non-receptor mediated effects, which are based on autoxidation of catecholamines in alkaline environment with a velocity increased by metal cations (Lassalle et al., 2003, Slominski et al., 2004c). The potential phenotypic implications are predominantly based on the well-documented activity of L-DOPA which through its oxidation products and active melanogenesis can affect functions of immune cells (Slominski and Goodman-Snitkoff, 1992, Slominski et al., 2009b). The possible mechanisms of action were discussed previously (Slominski et al., 1998c, Slominski et al., 2004c) and, therefore, have been shortly summarized below. L-DOPA dramatically inhibits an in vitro phosphorylation of glycoproteins dependent on the presence of Mn ions indicating action of quinones generated through oxidation of DOPA (Slominski and Friedrich, 1992). It can also affect cellular metabolism in melanotic cells (Scislowski et al., 1984, Scislowski et al., 1985). Also, diffusible products of DOPA oxidation are potent inhibitors of lipid peroxidation (Memoli et al., 1997), and 5-S-cysteinyldopa inhibits hydroxylation/oxidation reactions induced by the Fenton reaction (Napolitano et al., 1996). The potential cycling from indole to quinone forms of L-DOPA and its derivatives may affect levels of reactive oxygen/nitrogen species or oxidation of intracellular proteins and lipids (Tsang and Chung, 2009). Finally, both free

and protein-bound L-DOPA can trigger expression of several antioxidant enzymes including superoxide dismutase or NAD(P)H:Quinone oxidoreductase (NQO1) (Nelson et al., 2007). Thus, taking into consideration similar chemical properties of DOPA and catecholamines (products of DOPA enzymatic metabolism), and that their oxidation leads to the production of neuromelanin, one can safely conclude that non-receptor mediated effects and mechanisms will be similar to that described for DOPA (Slominski et al., 2011a). Taking into consideration the above chemical properties of dopamine, epinephrine or norepinephrine, one can expect that at micromolar or higher concentrations the predominant effects will be non-receptor mediated mainly through their oxidation products and neuromelanin polymers generated during this process. It is also possible that some of the phenotypic effects at lower concentrations could also be influenced by oxidative effects.

2.2.2.4. Conclusions: Dopamine, epinephrine and norepinephrine are produced in the skin resident and non-resident cells. Their phenotypic effects are mediated through activation of dopaminergic and adrenergic receptors, which expression is cell-type and -context dependent. Their roles in epidermal, dermal, and adnexal as well as skin immune functions remain to be further investigated. There are also non-receptor mediated mechanisms shared by their precursor, L-DOPA. It is likely that cutaneous catecholaminergic system will communicate with brain by activating sensory nerves, or, with other tissues, via entry into systemic circulation and by affecting immune cells circulating from the skin to other organs (Fig. 1).

2.3. Histamine

2.3.1. Production and metabolism of histamine—Histamine is derived from the decarboxylation of histidine by the L-histidine decarboxylase. After release, histamine is degraded by histamine-N-methyltransferase (in brain and at periphery) or diamine oxidase (in the periphery) (Fitzpatrick et al., 1993, Zhang et al., 2007). Histamine is produced mainly by mast cells and basophils. Cross-linking of IgE antibodies attached to the cell membrane represents a main mechanism for histamine release. Histamine binds to four different types of seven-transmembrane receptors that signal through G-proteins. The H_1 receptor is found on smooth muscle and endothelial cells and is responsible for smooth muscle contraction and decreased adhesion of endothelial cells. H_2 receptor is located on vascular smooth muscles and parietal cells in the stomach and is responsible for vasodilatation and gastric acid secretion. H_3 receptor is found in the central and peripheral nervous systems and is responsible for decreased secretion of several neurotransmitters including histamine, acetylocholine, serotonin and norepinephrine. H_4 receptor is found primarily on basophils and has a role in chemotaxis (Fitzpatrick et al., 1993, Zhang et al., 2007).

2.3.2. Bioregulatory role of histamine in the skin—In the epidermis, H_1 and H_2 receptors are expressed on keratinocytes (Albanesi et al., 1998, Koizumi and Ohkawara, 1999, Koizumi et al., 1998, Shinoda et al., 1998) and H_2 receptors on epidermal melanocytes (Yoshida et al., 2000). Mediators released from mast cells inhibit keratinocyte growth in culture (Huttunen et al., 2001). Activation of keratinocyte H_2 receptors affects proliferation and differentiation via activation of the cyclic AMP pathway and also phospholipase C pathway with associated increase in intracellular calcium levels (Koizumi and Ohkawara, 1999). In mouse keratinocytes, H_2 receptor signaling through the PLC second messenger system is inhibited during calcium–induced keratinocyte differentiation by an autocrine loop which involves down-regulation of H_2 receptor expression and inhibition of histamine metabolism (Fitzsimons et al., 2002). In keratinocytes, activation of the H_1 receptor enhances UVB-induced IL-6 production (Koizumi and Ohkawara, 1999, Koizumi et al., 1998), whereas H_1 receptor antagonists inhibit ICAM-1 expression (Ling et

al., 2004). Histamine upregulates keratinocyte MMP-9 production via the H_1 receptor (Gschwandtner et al., 2008). H_2, however, not H_1, agonists stimulate intracellular calcium signaling in keratinocytes (Koizumi and Ohkawara, 1999). In these cells, histamine acting on H1 receptors increases the expression of IFN-γ-induced intercellular adhesion molecule 1 (ICAM-1) and MHC class I molecules. It also augments IFN-γ-induced release of chemokines such as CXCL10, as well as the release of GM-CSF via protein kinase Cα and extracellular signal-regulated (ERK) kinase (Giustizieri et al., 2004, Kanda and Watanabe, 2004). In cultured keratinocytes, histamine through the activation of H_1 receptor inhibits CCL17 production by suppressing p38 MAP kinase and NF-κB activities. Histamine acts as a negative-feedback signal for existing Th2-dominant inflammation by suppressing CCL17 and enhancing CXCL10 production (Fujimoto et al., 2011). The effect of histamine acting through H2 receptor appears to be the opposite. Histamine, via H_2 receptor, increases survival of keratinocytes acting by NF-κB activation (Kim and Lee, 2010). IL-17, produced by Th17 cells infiltrating into the dermis (a cytokine involved in various inflammatory skin diseases including psoriasis) stimulates keratinocytes to produce inflammatory mediators such as IL-36, TNF-α, IL-6, and IL-8 (Carrier et al., 2011). Histamine markedly augments the production of IL-8 and GM-CSF in the presence of IL-17 and TNF-α in keratinocytes (Moniaga et al., 2011). Moreover, histamine induces human β-defensin 2 and 3 production in keratinocytes acting via H_1 receptors by activating NF-κB, AP-1 pathway, or STAT1, STAT3 and AP-1 as well as JAK2 and MEK/ERK signaling pathways (Ishikawa et al., 2009, Kanda and Watanabe, 2007). Histamine promotes cutaneous antimicrobial defenses and wound repair by stimujlating secretion of defensins (Ishikawa et al., 2009, Kanda and Watanabe, 2007). Histamine also enhances nerve growth factor production by inducing c-Fos expression in keratinocytes (Kanda and Watanabe, 2003).

The activation of the H_2 receptors on melanocytes stimulates melanogenesis (Yoshida et al., 2000). Histamine, similarly to α-MSH, contributes to hyperpigmentation by enhancing eumelanin/pheomelanin ratio (Lassalle et al., 2003). Acting at the H_2 receptor histamine stimulates melanocyte migration in culture via signaling through ERK, CREB, and Akt (Kim and Lee, 2010). Histaminergic system is up-regulated in the B16F10 melanoma cells when compared to non-cancerous melanocytes, what indicates that it might have a role in tumorigenesis (Davis et al., 2011). Both Western blot and immunohistochemical studies showed much stronger histidine decarboxylase expression in melanoma cells as compared to normal melanocytes (Haak-Frendscho et al., 2000). Moreover, H_1 histamine receptor antagonists were shown to induce genotoxic and caspase-2-dependent apoptosis in human melanoma cells, but not normal melanocytes (Jangi et al., 2006).

In the dermis, histamine receptors are expressed on fibroblasts, immunocytes, endothelial cells, blood vessels, smooth muscle, and nerve endings (Fitzpatrick et al., 1993). In Th2 lymphocytes stimulation of H_4 receptor led to the activation of transcription factor AP-1 followed by the release of IL-31, that is involved in the development of pruritus (Gutzmer et al., 2009). On the other hand, activation of H_4 histamine receptors expressed on monocytes activated intracellular calcium mobilization and inhibited the CCL2 chemokine production which reduced recruitment of monocytes (Dijkstra et al., 2007). Histamine acts on H_4 receptors of eosinophils and mediates their chemotaxis, induces cell shape change and upregulates adhesion molecules CD11b/CD18 (Mac-1) and CD54 (ICAM-1). This effect, while observed in cultured eosinophils, may be of a paramount importance in the skin (Ling et al., 2004).

Histamine also acts on H_2 and H_4 receptors of plasmacytoid dendritic cells and downregulates production of TNF-α, IFN-α and CXCL8 (Mazzoni et al., 2003). Plasmacytoid dendritic cells migrate in response to H_4 receptor agonist stimulation. Of note,

H_4 receptor is present in high levels on plasmacytoid dendritic cells in the lesional psoriatic skin (Gschwandtner et al., 2008).

2.3.3. Conclusions—Histamine is produced not only by mast cells but also by other cells of epidermis and dermis and acts locally in the epidermis and dermis by binding to H_1-H_4 receptors. Histamine targets not only endothelium and smooth muscles of blood vessels but also modulates function of keratinocytes, melanocytes and cells of skin immune system. It affects intracellular signaling cascades, cell proliferation and melanogenesis. Histamine is upregulated in melanoma cells. It signals mainly via H_4 receptor on the cells of the immune system and affects their migration and cytokine secretion patterns. Moreover, it modulates Th2 type immune responses and antimicrobial peptide expression. Thus, histamine is an important part of the neuro-immunoendocrine system of the skin (Slominski and Wortsman, 2000) with local and systemic effects (Figs. 1, 2).

2.4. Serotoninergic system

2.4.1. Production and metabolism of serotonin (Fig. 5)

2.4.1.1. An overview: Serotonin (5-hydroxytryptamine, 5-TH) is widely synthesized throughout the animal kingdom, plants and unicellular organisms (Azmitia, 2001, Azmitia, 2007). In plants serotonin serves as a trophic factor and an antioxidant which is similar to the animal kingdom (Azmitia, 2001). In humans serotonin was shown to be synthesized predominantly by intestinal enterochromafin cells with other sites of production represented by the central nervous system, pineal gland, retina, ovaries, placenta, thymus, pancreas, skin, breast, gestational tissues, blood vessels, rectal epithelium, bronchial epithelial cells, thyroid parafollicular cells, mast cells and lymphocytes (Nordlind et al., 2007).

The first obligatory step in the synthesis of serotonin is the hydroxylation of L-tryptophan to produce 5-hydroxytryptophan (TrpOH) in a reaction catalyzed by tryptophan hydroxylase (TPH) (Mockus and Vrana, 1998), a protein encoded either by ubiquitously expressed TPH1 gene (Mockus and Vrana, 1998) or TPH2 gene expressed predominantly in the brain (Zhang et al., 2004). This reaction requires oxygen and co-factor 6BH4. TrpOH is further decarboxylated by AAD to produce 5-HT. In humans L-tryptophan is present in blood plasma at steady-state level both in the free form (approximately $1.2x10^{-5}$ M) and bound to serum albumins (ca. $6x10^{-5}$ M), with TPH having a Kd for tryptophan of approximately 10^{-8} M. Thus, fluctuations in free pool of tryptophan directly and immediately alter the level of serotonin synthesis (Nordlind et al., 2007). Catabolism of serotonin is initiated by MAO with the production of 5-hydroxyindoleacetaldehyde, oxidized further by aldehyde dehydrogenase (E.C. 1.2.1.3) to 5-hydroxyindole-3-acetic acid (5HIAA), which is the main product of metabolism, or reduced to 5-hydroxytryptophol (HTOL) by alcohol dehydrogenase (E.C. 1.1.1.1) (Fig. 5). 5-HT can also be methylated to 5 methoxytryptamine (5MTT) and catabolized as shown in Fig. 5. Additional pathway involves serotonin acetylation by arylalkylamine N-acetyltransferase (AANAT) or arylamine N-acetyltransferase isoenzyme showing substrate specificity towards both arylamines and arylakylamines to produce N-acetylserotonin (NAS) (Fitzsimons et al., 2002, Klein, 2004). NAS can also be further metabolized to melatonin (Reiter, 1991). In the skin a number of NAS metabolites unrelated to melatonin were found, which nature and mechanism of generation remain to be defined (Slominski et al., 2003b). After release into blood, serotonin is actively taken up into platelets and stored in solid granules with a help of a serotonin transporter (5HTT), a member of the Na+/Cl−-dependent transporter superfamily, which actively regulates serotonin transport. Serotonin can be transported through the plasma membrane in either direction, however, under most conditions, its reuptake is favored (Nordlind et al., 2007). Plasma serotonin is also cleared by the liver and lung endothelial cells and further catabolized to 5HIAA.

2.4.1.2. Production and metabolism of serotonin in the skin: Mammalian skin cells can produce serotonin via the sequential transformation of L-tryptophan by TPH and AAD (Slominski et al., 2005c) (Fig. 5). Thus, the *TPH1* gene is expressed in human skin under normal and pathological conditions as well as in a wide array of normal and transformed human epidermal, dermal and adnexal skin cells with some cells expressing the aberrant *TPH1* transcript (Slominski et al., 2003b, Slominski et al., 2002c). As to the *TPH2* gene, it is expressed in the retinal pigment epithelium (Zmijewski et al., 2009b) and normal and malignant melanocytes (Zmijewski and Slominski, unpublished). Although the *TPH* gene is expressed almost in all types of human skin cells the highest expression was found in normal and malignant melanocytes that also accumulated significant amounts of serotonin (Figs. 6, 7) (Slominski et al., 2003a, Slominski et al., 2005c). Interestingly, the enzymatic conversion of tryptophan to TrpOH in melanoma cells occurs at high levels, comparable to those in the brain (Slominski et al., 2002a, Slominski et al., 2002c). TPH and *TPH1* were also detected in the mouse and hamster skin, and in cultured mouse follicular melanocytes and melanoma cells (Slominski et al., 2002a, Slominski et al., 2003b). Interestingly, the *TPH1* gene expression changes during murine hair cycle (Slominski et al., 2003b). In addition, TPH and serotonin are strongly expressed in rodent masts cells. It is also important to notice that the skin has a capability for de novo synthesis/recycling of the 6BH4 (Schallreuter et al., 2008a, Schallreuter et al., 1998, Schallreuter et al., 1997) and of pyridoxal 5′-phosphate (PLP) (Coburn et al., 2003) both serving as important co-factors necessary for the production of TrpOH and serotonin. Interestingly, non-enzymatic production of TrpOH through H_2O_2 and UVA irradiation indicates that a free-radical-mediated oxidation of L-tryptophan is also possible in the skin (Schallreuter et al., 2008a).

In human skin biopsies immunoreactivity of TPH and serotonin was found in normal epidermal melanocytes and malignant melanomas (Figs. 6, 7) (Slominski et al., 2003a) with additional detection by immunofluorescence techniques in epidermal keratinocytes, hair follicles, eccrine glands, blood vessels and skin mast cells (Slominski et al., 2005c). These findings are consistent with the immunodetection of serotonin in perivascular human mast cells of adrenal cortex (Lefebvre et al., 2001) and breast epithelial cells (Matsuda et al., 2004). Serotonin was also detected by immunocytochemistry in dermal Merkel cells in rat and pig skin at the epidermal rete ridges and upper hair follicles adjacent to nerve terminals (Nordlind et al., 2008). Cutaneous serotonin content can be affected by inflammatory processes (Lonne-Rahm et al., 2008, Nordlind et al., 2008, Rasul et al., 2011, Thorslund et al., 2009). For example, human skin affected by psoriasis or chronic eczema showed elevated expression of serotonin in the epidermal and adnexal structures (Nordlind et al., 2007; 2008)

The catabolism of serotonin in mouse skin is initiated by its deamination by MAO, followed by the oxidation or reduction of the resultant 5-hydroxyindole acetaldehyde to 5HIAA and/or 5HTPOL (Slominski et al., 2003b). Similar metabolism was uncovered in rat skin, although in this species 5HIAA was the main degradation product and 5-HTPOL remained below the limit of detectability (Semak et al., 2004). MAO metabolism of serotonin was also detected in guinea pig skin (Tachibana et al., 1990b) and production of 5HIAA was documented in human epidermal keratinocytes and melanoma cells (Slominski et al., 2002c).

The alternative serotonin metabolism pathway in the skin is represented by its acetylation to N-acetylserotonin, which in human and rodent skin and cultured skin cells is mediated via the action of either AANAT or NAT with mixed arylamine/arylalkylamine substrate specificity (Slominski et al., 2005c). In hamster skin we characterized two N-acetyltransferase activities including NAT-1 with substrate specificity towards arylamines, and NAT-2 showing substrate specificity towards both arylamines and arylalkylamines such

as serotonin, tryptamine, and methoxytryptamine (Gaudet et al., 1993, Slominski et al., 2002a). Furthermore, we demonstrated that at least part of this activity in hamster, rat and human skin represented native AANAT (Slominski et al., 2002a). In accordance, serotonin N-acetyltransferase activity was significantly inhibited by low concentrations of coenzyme A-S-N-acetyltryptamine (Cole bisubstrate; BSI, see (Hickman et al., 1999, Khalil et al., 1998)) indicating true AANAT activity. However, significant enzymatic activity generating NAS was resistant to BSI suppression, showing that in rodents arylamine activity (NAT-2) resistant to BSI can also participate in the acetylation of serotonin (Semak et al., 2004, Slominski et al., 2002a). Rodent NAT-2 is a homologue of human NAT-1, thus, it is likely that NAT-1 may contribute to NAS production also in the human skin. Interestingly, in the C57BL/6 mouse producing inactive AANAT (Roseboom et al., 1998b), we detected cutaneous transformation of serotonin to NAS and, to a lesser extent, acetylation of tryptamine (Slominski et al., 2003b). Most interestingly, acetylation of serotonin, but not of tryptamine, was dependent on the phase of hair cycle, skin anatomic location and the presence of pathology (melanoma). NAS was further metabolized to several products (of which chemical nature remains to be defined) in a hair cycle dependent fashion (Slominski et al., 2003b). In humans, both skin racial pigmentation and cutaneous pathology determine the reaction rate and specificity of serotonin acetylation (Slominski et al., 2002c).

2.4.2. Bioregulatory role of serotonin in the skin—Serotonin regulates a wide range of physiological processes at the central and peripheral levels acting as a neurotransmitter, hormone, cytokine, biological modifier, growth factor, morphogen and anti-oxidant or pro-oxidant (Azmitia, 2007, Azmitia, 2010). The above functions are mediated through receptor-dependent and -independent mechanisms (Hoyer et al., 2002).

Serotonin acts via multiple receptor subtypes labeled as 5-HT1 through 5-HT7 (Hoyer et al., 2002). Most of these receptors are metabotropic, with the exception of 5-HT3, which is ionotropic and primarily gates sodium and potassium ions. 5-HT1 receptors (1A, 1B, 1D, 1E and 1F) couple via Giα to inhibit cAMP formation while 5-HT4, 5-HT6 and 5-HT7 all couple via Gsα to stimulate cAMP production (Hoyer et al., 2002). In addition, 5-HT1A receptors produce membrane hyperpolarization by coupling to K^+-channels. 5-HT2 (2A, 2B and 2C) receptors couple via Gqα to phosphatidylinositol hydrolysis and the formation of inositol trisphosphate and diacylglycerol (Hoyer et al., 2002). The 5-HT5 receptor (5A and 5B) is considered to be an orphan receptor. Serotonin receptor function can be modulated by RNA editing, endogenous lipids that act as allosteric modulators, and serotonin moduline (tetrapeptide, 5-HT-moduline) that is produced by proteolytic modification of chromogranin. 5-TH-moduline is an allosteric modulator which regulates 5-HT5 receptors dimerization and formation of either homodimers or heterodimers. The receptors heterogeneity and functional diversity is also amplified by the process of alternative splicing and differential subunit incorporation into the receptor complex. The regulation of 5-HT receptor activity is also affected by serotonin transporters, which remove serotonin from the extracellular environment or, under certain conditions, pump it out of the cell.

In human skin and skin cells we identified expression of genes coding 5-HT receptors, including *HTR1A*, *1B, 2A, 2B, 2C*, and *7* genes and it was shown that pattern of expression was cell type specific and modified by skin pathology (Slominski et al., 2003c). Interestingly, alternatively spliced form of *HTR2C* with a deletion of exon 2, fragment of exon 3 and an insertion of cryptic exon containing termination codon was found in human melanoma, while the *HTR2B* isoform with a deletion of exon 2, but with a preserved reading frame coding for a receptor protein without transmembrane domains 3 and 4 was found in normal human skin and skin affected by basal cell carcinoma (Slominski et al., 2003a). We also found RNA editing (A to G substitution) in human *HTR7* gene (Slominski et al., 2003a), which may be connected to the local expression of adenosine deaminases (Liu

et al., 1999). In mouse and hamster skin expression of the *HTR2B* and *HTR7* genes was demonstrated, which was dependent on the phase of hair cycle (mouse) and type of tissue or cells (Slominski et al., 2004b).

We should also mention that Kaneko et al have failed to detect 5-HT2A gene in epidermal keratinocytes (Kaneko et al., 2009). However, these findings have to be considered with caution, since other researchers demonstrated that 5-HT2A antagonists inhibited UVR-induced skin carcinogenesis (Sreevidya et al., 2010, Sreevidya et al., 2008) and that sunlight-induced immunosuppression could be mediated via the activation of 5-HT2A by cis-urocanic acid (Walterscheid et al., 2006). Furthermore, 5-HT2A protein was detected by immunocytochemistry in dermal lymphocytes, fibrocytes, vasculature and sensory nerve endings, abating the epidermis (Nordlind et al., 2008), while 5-HT1A receptor was localized to keratinocytes of the upper epidermis, epidermal melanocytes, mast cells and dermal vasculature (Nordlind et al., 2008). Furthermore, 5-HT1A and 5-HT2A were detected in the majority of benign tumors such as compound nevi, dysplastic nevi and also in malignant melanomas (Nordlind et al., 2008). By the use of immunocytochemistry, 5-HT2C was detected in epidermal Langerhans cells and melanocytes, 5-HT3 in the basal epidermal keratinocytes and 5-HT7 in dermal vasculature (Nordlind et al., 2008). 5-HT1A, 2A and 2C were also detected in rodent skin dermal and epidermal immune cells (Nordlind et al., 2008). Diverse expression of 5-HT receptors was also found in immune cells that was dependent on cell type and their level of activation.

Also Merkel, Langerhans and mast cells, lymphocytes and macrophages (Nordlind et al., 2008), and immortalized human epidermal keratinocytes and melanoma cells express 5-HTT (Fig. 6). Their role is substantiated by observations which showed that serotonin uptake inhibitors could induce spontaneous bruising, pruritus, urticaria, angioedema, erythema multiforme, the Steven–Johnson syndrome, toxic epidermal necrolysis, erythema nodosum, alopecia, hypertrichosis, leukocytoclastic vasculitis and acneiform eruption (reviewed by Nordlind et al., 2008, Slominski et al., 2005c). This can also be associated with flares of psoriasis vulgaris and development of delayed hypersensitivity.

Under in vitro conditions, serotonin exerted variable effects on skin cells depending on the context (Nordlind et al., 2008, Salim and Ali, 2011, Slominski et al., 2005c). It stimulated proliferation of dermal fibroblasts (Slominski et al., 2005c), similarly to non-skin fibroblasts (Seuwen et al., 1988; Seuwen and Pouyssegur, 1990; David, 1991; Nebigil et al., 2000). Serotonin also stimulated growth of epidermal melanocytes in the absence of growth factors, while inhibiting their proliferation in media supplemented with serum (Slominski et al., 2003a). The former effect could be linked with the stimulation of intracellular cAMP accumulation, while the latter could represent serotonin antagonism with serum growth factors (Slominski et al., 2005c). NAS, the product of serotonin metabolism, showed no effect on the proliferation of fibroblasts and melanocytes (Slominski et al., 2003a) and serotonin or inhibitors of its uptake inhibited melanogenesis (reviewed in Slominski et al., 2004e, Slominski et al., 2005c). In addition, serotonin modulated proliferation of cultured murine keratinocytes (Maurer et al., 1997). Interestingly, serotonin content within mast cell granules steadily decreased throughout anagen and increased during catagen and telogen phases of hair cycle (Hasse et al., 2007).

Serotonin shows vasoactive and immunomodulatory effects. For example, it plays a role in the Arthus reaction (Tachibana et al., 1990a, Yuasa et al., 2001), induces sustained vascular permeability (Fujii et al., 1994), and also modulates the inflammatory response to substance P (SP) via capsaicin-sensitive sensory fibers (Khalil and Helme, 1990). Serotonin participates in the activation of T cells and natural killer cells by macrophages, initiation of delayed-type hypersensitivity responses, production of chemotactic factors, and the

modification of innate immune responses (Benton et al., 2010, Betten et al., 2001, Cloez-Tayarani and Changeux, 2007, Hsueh et al., 2002, Mossner and Lesch, 1998). In allergic contact dermatitis and psoriasis, number of cells expressing both 5-HT1A and tryptase diminishes, whereas the number of dermal cells expressing 5-HT2A and CD3 increases, including atopic dermatitis (Lonne-Rahm et al., 2008, Nordlind et al., 2008, Rasul et al., 2011, Thorslund et al., 2009). Similar pattern is found in the murine epidermis affected by contact eczema. Furthermore, both eczematous and psoriatic human skin shows increased number of mononuclear cells expressing 5-HTT (reviewed by Nordlind et al., 2008). In addition, serotonin can act as a chemoattractant for eosinophils, probably by binding to 5-HT2A receptors. It is involved in the mast cells recruitiment of to the site of tissue injury through the activation of 5-HT1A, however, without inducing their degranulation (Nordlind et al., 2008). Regulatory function of 5-HT1A in inflammatory responses is emphasized by the suppression of the severity of contact allergy in rats, after topical or oral administration of its agonist, buspirone (Nordlind et al., 2008). Another 5-HT1A agonist, tandospirone, attenuates itching in patients with atopic dermatitis (Nordlind et al., 2008). On the other hand, treatment with 5-HT2A antagonists reduced the severity of contact allergic reactions in mice and one of them, spiperone, was effective when applied either systemically or topically. Furthermore, 5-HT2 receptor antagonist, ketanserin, inhibited the established, but not challenge-induced phases of allergic contact dermatitis (Nordlind et al., 2008). Serotonin is also involved in the pathogenesis of cholestatic and uremic pruritus, urticaria, and itch reaction (reviewed by Slominski et al., 2005c).

2.4.3. Serotonin receptors on sensory nerves—5-HT receptors were widely detected on cutaneous sensory nerve endings (reviewed by Nordlind et al., 2008, Slominski et al., 2005c). Intradermal injection of serotonin into rat elicited enhanced c-fos-like immunoreactivity in superficial lamina at the lateral aspect of the dorsal horn, in a manner similar to the immunoreactivity evoked by capsaicin. The 5-HT receptor were detected in unmyelinated sensory axons at the dermal-epidermal junction and the nerve endings of Pacinian corpuscles of rat glabrous skin (Carlton and Coggeshall, 1997) and rat sinus hair follicle (Tachibana et al., 2005). 5-HT1 receptors are present in the dermis of rabbits on afferent nerve fibers around hair follicles and sebaceous glands (Branchek et al., 1988). 5-HT2A receptors are partially responsible for mediating scratching in mice (Tachibana et al., 1990b). Although neither 5-HT2 nor 5-HT3 appear to be involved in itch responses caused by chronic allergic skin dermatitis in rats, acute scratching is mediated by skin 5-HT2 receptors, and intradermal injection of serotonin induced itching in normal, but not inflamed skin (reviewed by Nordlind et al., 2008, Slominski et al., 2005c). In human skin, 5-HT2A and 5-HT3 are localized on sensory nerve ending in the dermis or located close to or entering the epidermis, and their activation may explain pruritic responses to intradermally injected serotonin (Nordlind et al., 2008, Slominski et al., 2005c). Specifically, an antagonist of 5-HT3, ondansetron, can reduce the severity of pruritus, while paroxetine is used in the treatment of pruritus and its antipruritic action is connected with down-regulation of 5-HT3 expression (Nordlind et al., 2008, Slominski et al., 2005c).

2.4.4. Reception of ultraviolet light—The cutaneous serotoninergic system may play a role in body reception of and reaction to light (Slominski et al., 2005c). For example, it has been reported that UVA-induced well-being can be linked to increased serum serotonin and decreased melatonin levels after a single radiation exposure (Gambichler et al., 2002). It has also been proposed that 5-HT2A plays a role in the transduction of UVR energy into biological responses by serving as the receptor for cis-urocanic acid (cis-UCA), generated through photoisomerization of the trans-UCA in the stratum corneum after absorption of UVR (Walterscheid et al., 2006). Cis-UCA acts as a powerful local and systemic immunosuppressor (Garssen et al., 2001), and it was proposed that 5-HT2A mediates

immunosuppressive effects of UVR after binding of cis-UCA (Walterscheid et al., 2006). A role for 5-HT2A in UVB-induced skin photocarcinogenesis, was also suggested (Sreevidya et al., 2010, Sreevidya et al., 2008). Other authors proposed that cis-UCA and serotonin mediate UVB-induced immunomodulation, however, via independent pathways in which cis-UCA does not act through 5-HT2A (Kaneko et al., 2009). Thus, there is sufficient information to support involvement of the local serotoninergic system in cutaneous responses to the UV light, however, the mechanism may be more complex than originally anticipated. It may include activation of 5-HT receptor- signaling on either nerve ending or skin cells secondary to UVR-induced local production of serotonin or alternative ligands for HT-receptors with a consequent regulation of local homeostasis and immune system. Such signals will be projected to the brain via the ascending nerve routes. Furthermore, release of serotonin into circulation may generate endocrine effects.

2.4.5. Conclusions—The mammalian skin cells have the capability to produce and metabolize serotonin. The cutaneous phenotypic effects are mediated by its interactions with 5HT receptors including 5-HT1A, 1B, 2A, 2B, 2C, 3 and 7 and 5-HTT receptors, which are expressed in a cell type-dependent manner. The serotonin receptors are also expressed on sensory nerve endings, which transmit to the brain information on changes in skin homeostasis induced by either intrinsic or environmental factors (Slominski, 2005, Slominski and Wortsman, 2000). The topical application of specific receptors agonists or antagonists, serotonin uptake inhibitors or modulation of local serotonin production/degradation may represent future novel therapies of skin diseases including neurodermatoses and itching disorders. Finally, the cutaneous serotoninergic system may be involved in the transformation of light energy of solar radiation into local and systemic biological responses, with the latter mediated via transmission to brain, endocrine effects or regulation of systemic responses as shown on Figs. 1 and 2.

3. MELATONINERGIC SYSTEM IN THE SKIN

3.1. Melatonin Production

Melatonin production is highly conserved in nature through different species including bacteria, unicellular eukaryotes, algae, plants invertebrates and vertebrates (Hardeland et al., 2011, Reiter, 1991, Slominski et al., 2008a, Tan et al., 2002, Yu and Reiter, 1993). In mammals, melatonin is produced in the pineal gland (Reiter, 1991) as well as in brain, retina, Harderian gland, ciliary body, lens, thymus, airway epithelium, bone marrow, immune cells, gonads, placenta, gastrointestinal tract and skin (Bubenik, 2002, Carrillo-Vico et al., 2004, Hardeland et al., 2011, Kanda and Watanabe, 2007, Pandi-Perumal et al., 2006, Slominski et al., 2005a, Slominski et al., 2008a, Watson S, 1994, Zmijewski et al., 2009b), and perhaps other organs. Circulating melatonin predominantly derives from the pineal gland by diffusion into the circulation, although entry from other extra-pineal sites of production is also possible.

Melatonin is a product of a two-step transformation of serotonin which involves acetylation catalyzed by AANAT to NAS (a rate limiting step) followed by methylation by hydroxyindole-O-methyltransferase (HIOMT, EC 2.1.1.4) to produce melatonin (N-acetyl-5-methoxytryptamine) (Reiter, 1991, Yu and Reiter, 1993). In the pineal gland melatonin production is controlled by the suprachiasmatic nucleus through nocturnal sympathetic release of norepinephrine that acting via adrenergic receptors activates cAMP dependent signal transduction cascades leading to the stimulation of AANAT and ultimate production of melatonin (Klein, 2007, Reiter, 1991, Yu and Reiter, 1993). Melatonin synthesis is also potentiated by vasoactive intestinal peptide (VIP), pituitary adenylate cyclase-activating peptide (PACAP) and neuropeptide Y (Klein, 2007, Reiter, 1991, Yu and Reiter, 1993). NAS can also be produced by the action of arylamine N-acetyltransferases

(Fitzsimons et al., 2002) as it was shown in human (Slominski et al., 2002c), rat (Semak et al., 2004), hamster (Gaudet et al., 1993, Slominski et al., 2002a) and murine skin (Slominski et al., 2003b). NAS can be further methylated to melatonin, depending on the anatomic location and activity of HIOMT. This is best illustrated in the C57BL/6 mice, defined by some authors as a natural melatonin "knockdown" (Kobayashi et al., 2005, Roseboom et al., 1998a, Slominski et al., 2003b). Specifically, in the C57BL/6 mouse serotonin can be acetylated to NAS in a reaction mediated by an enzyme different from conventional AANAT providing an important mechanistic explanation for the significant production of melatonin in the peripheral organs of this species, which express HIOMT (Ma et al., 2008, Scarparo et al., 2000, Slominski et al., 2003b). In addition, the existence of low flux rate alternative pathways have been proposed that involves O-methylation of serotonin with subsequent N-acetylation, or O-methylation of tryptophan followed by consecutive decarboxylation and N-acetylation.

Transcripts of *AANAT* and of *HIOMT* genes were detected in normal and pathological skin biopsies, and in most skin cells cultured in vitro including normal keratinocytes (neonatal and adult, epidermal and follicular), immortalized HaCaT keratinocytes, fibroblasts (dermal and hair follicle papilla), normal melanocytes, several melanoma cell lines and squamous cell carcinoma cells (Slominski et al., 2002b). Interestingly, novel isoforms of *AANAT* and *HIOMT* were detected in normal and pathological skin (invaded by basal cell carcinoma cells) and in neonatal keratinocytes (Slominski et al., 2002b). Gene expression in epidermal and dermal skin cells was followed by the synthesis of the AANAT and HIOMT enzymes with the detection of corresponding enzymatic activities (Slominski et al., 2002b).

The acetylation of serotonin was also dependent on local cellular environment. Thus, when AANAT activity was calculated for two substrates, tryptamine and serotonin, the activity ratios were close to 1 for all melanoma lines and for keratinocytes. On the other hand, these ratios ranged from 2.5 to 6 for whole skin from three white subjects and zero in melanocytes and in whole skin of a black subject whose AANAT activity towards tryptamine was below detectability level. These finding suggests a role for both skin racial pigmentation and type of cutaneous pathology (such as melanoma) in this regulation (Slominski et al., 2002b). Both of them may be important determinants of reaction rate and specificity of serotonin acetylation. Using immunocytochemistry AANAT antigen was detected in suprabasal differentiating keratinocytes in human scalp epidermis. However, melanocytes also exhibited immunoreactivity for this enzyme (Fig. 7). High expression of the antigen was also seen in the outer peripheral epithelial layers of the anagen hair follicles (Fig. 7) and the basal cells of the sebaceous and eccrine glands. The expression was further found in sensory nerve endings abutting the epidermal layers (Slominski et al., 2005c). Melatonin-like immunoreactivity in human skin was detected on differentiating keratinocytes in spinous and granular layers of the epidermis (Fig. 7). The antigen was not expressed in keratinocytes of basal and suprabasal layers of the epidermis, while being found in singly-scattered melanocytes. Melatonin-immunoreactivity was also detected throughout the hair follicle epithelium, in blood vessels and cutaneous mast cells (Slominski et al., 2005c). These findings were further confirmed by the detection of NAS and melatonin using tandem liquid chromatography/mass spectrometry (LC/MS) in epidermal cells (Slominski et al., 2002a, Slominski et al., 2002c) and hair follicles (Kobayashi et al., 2005). These findings showed that human skin, in addition to the pineal gland and retina, possesses the intrinsic capability to synthesize melatonin (Abe et al., 1999, Carrillo-Vico et al., 2004, Finocchiaro et al., 1991, Itoh et al., 1999, Scarparo et al., 2000). Importantly, this cutaneous melatoninergic pathway operates in a compartment-specific manner since it is localized mainly to the epidermal, adnexal and dermal cell populations (Fig. 7) (Slominski et al., 2008a).

Similar capability to produce melatonin was demonstrated in rodent skin (Slominski et al., 2005c). For example, in hamster skin fragments maintained ex-vivo serotonin was transformed into melatonin with NAS as the intermediate product (Slominski et al., 1996b, Slominski et al., 2002a). This transformation was time- and dose-dependent, and was stimulated by forskolin - indicating involvement of cAMP signal in this process (Slominski et al., 1996b). These findings have been confirmed in follow-up studies (Slominski et al., 2005c). Specifically, biochemical assays in mouse, rat and hamster skin clearly demonstrated that skin of all of these species can transform serotonin to NAS, the obligatory precursor for melatonin (Semak et al., 2004, Slominski et al., 2002a, Slominski et al., 2003b). Additionally, murine skin in organ culture and mouse vibrissae hair follicles can produce melatonin and its synthesis was enhanced by the addition of norepinephrine (Kobayashi et al., 2005). Interestingly, detailed analysis with bisubstrate Cole inhibitor in combination with molecular analyses showed that in rodent skin NAS production was initiated by both AANAT and NAT (Semak et al., 2004, Slominski et al., 2002a), while in C57BL6 mouse NAS appeared to be only produced by NAT (Slominski et al., 2003b). This latter finding provides mechanistic explanation for melatonin production in C57BL/6 mice at selected extracranial sites, which would require HIOMT expression since NAS produced via AANAT-independent pathways could serve as substrate for HIOMT-mediated transformation into melatonin (Ma et al., 2008, Scarparo et al., 2000, Slominski et al., 2003b). Our enzymatic studies excluded corporal skin of the C57BL/6 mouse in vivo as a site of melatonin production, although we detected low levels of HIOMT activity in mouse ear (Slominski et al., 2003b).

3.2. Melatonin degradation

Melatonin can be degraded via indolic and kynuric pathways. The first one involves 6-hydroxylation by CYP1A1, CYP1A2 or CYP1B1 to 6-hydroxymelatonin (predominantly in the liver), which after sulfatation or glucuronidation is excreted in urine (Kopin et al., 1961, Ma et al., 2008, Ma et al., 2005). In the liver, the intrinsic clearance for melatonin hydroxylation by high-and low-affinity components indicated that both mitochondrial and microsomal cytochrome P450s metabolize melatonin principally by 6-hydroxylation, with O-demethylation representing minor metabolism (Ma et al., 2005). In addition, melatonin deacetylase produces 5-methoxytryptamine that is oxidized by monoamine oxidase to form 5-methoxyindoleacetaldehyde, which is converted to 5-methoxyindole acetic acid by aldehyde dehydrogenase or to 5-methoxytryptophol by alcohol dehydrogenase (Cahill and Besharse, 1989, Grace et al., 1991). In the kynuric pathway, melatonin can be converted either enzymatically or non-enzymatically to N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK), in a process that encompasses generation of 3-hydroxymelatonin, 2-hydroxymelatonin, melatonin 2-indolinone, 3-hydroxymelatonin, 2-indolinone, and melatonin dioxetane as intermediate products (Hardeland et al., 2009, Hirata et al., 1974, Reiter et al., 2007). AFMK synthesis involves enzymes or pseudoenzymes such as cytochrome c, horseradish peroxidase, indoleamine dioxygenase, myeloperoxidase, oxoferryl hemoglobin or hemin as well as non-enzymatic pathway that may be activated in the presence of reactive oxygen species (ROS) or UVB (Fischer et al., 2006a, Hardeland et al., 2009, Kanda and Watanabe, 2007, Seever and Hardeland, 2008, Semak et al., 2008, Semak et al., 2005). In addition, catalase, arylamine formamidase, hemoperoxidase and ROS can stimulate the conversion of AFMK to AMK (Hardeland et al., 2009, Kanda and Watanabe, 2007, Reiter et al., 2007). Melatonin can also be demethylated to NAS by CYP2C19 or CYP1A2 (Semak et al., 2008). However, according to some authors, AFMK and AMK pathways of melatonin metabolism are insignificant at the systemic level in mouse (Ma et al., 2008).

Melatonin metabolites 5-methoxytryptamine (5MTT) and 5-methoxytryptophol (5MTOL) have been detected in cultured mammalian skin fragments and melanoma cells (Slominski et al., 1996b, Slominski et al., 2002b, Slominski et al., 2002c) indicating similarity in the degradative pathways of melatonin metabolism in frog skin and retina (Cahill and Besharse, 1989, Grace et al., 1991), including the activity of monoamine oxidase (MAO) in mammalian skin (Semak et al., 2004, Slominski, 2005b). It was shown that cutaneous degradation of melatonin may also include pathways known to be operative in the liver and kidney (Grace et al., 1991, Kanda and Watanabe, 2007, Pandi-Perumal et al., 2006) with 6-hydroxymelatonin production as an intermediate (Fischer et al., 2006a). This shows that indolic degradative pathway is operating in the skin (Fischer et al., 2006a, Slominski et al., 1996b). However, experiments with cultured human immortalized keratinocytes have shown that melatonin is mostly metabolized to 2-hydroxymelatonin and AFMK by the kynuric pathway or through direct non-enzymatic action of UVB (Fischer et al., 2006a). Interestingly, UVB also induces AFMK utilization by keratinocytes, suggesting the involvement of arylamine formamidase in the further metabolism of AFMK to AMK (Fischer et al., 2006a). Based on the above, together with the known mechanism for melatonin degradation or transformation in peripheral organs, we proposed that in the skin melatonin can be metabolized via alternative pathways including non-enzymatic reactions (Fig. 8). These would exhibit species-, site-, tissue- and cell compartment- as well as cell type-dependent differences, subjected to further modulation by environmental factors including UVR (Fischer et al., 2008b, Slominski et al., 2008a). Pathways' activities and the nature of the final product would be linked to the spatial distribution of melatonin in the skin, to the specific cell type and sub-cellular compartments, where the biological activity of melatonin would either be attenuated due to its degradation or be amplified by the generation of even more potent metabolites, such as AFMK or AMK (Fischer et al., 2008b, Slominski et al., 2008a).

3.3. Biological activity of melatonin

At the central level, melatonin functions as chronobiotic regulator (Zeitgeber; circadian pacemaker) regulating photoperiod-dependent reproduction and other biological rhythms, as well as a prominent sleep promoter (reviewed by Pandi-Perumal et al., 2006, Reiter, 1991, Watson S, 1994, Yu and Reiter, 1993). It plays a role in reproduction and sexual maturation, energy expenditure and body mass regulation, acting via central or peripheral receptors (Hardeland et al., 2011, Pandi-Perumal et al., 2006, Reiter, 1991, Watson S, 1994, Yu and Reiter, 1993). Melatonin can additionally affect brain and immune, GI, cardiovascular, renal, bone and endocrine functions. It shows also oncostatic, anti-aging and cell-protective activities (Bartsch et al., 2002, Bubenik, 2002, Hardeland et al., 2011, Jung and Ahmad, 2006, Luchetti et al., 2010, Pandi-Perumal et al., 2006, Reiter, 1991, Watson S, 1994, Yu and Reiter, 1993). Thus, melatonin has pleiotropic bioactivities acting as a neurotransmitter, hormone, cytokine and biological response modifier. These functions are mediated by interactions with high affinity receptors (Dubocovich et al., 2003, Hardeland et al., 2011, Pandi-Perumal et al., 2006, Reiter, 1991, Yu and Reiter, 1993). The proposed actions of melatonin or its metabolites in the skin are shown in Figure 9.

Melatonin exerts its effects by interacting with specific receptors that are widely distributed throughout the body, and which are differentially expressed in various organs and tissues (Dubocovich et al., 2010, Dubocovich et al., 2003). The cell surface receptor family comprises MT1 (MTNRa) and MT2 (MTNRb) whose coding region genomic structure is similar and constitutes two exons and one intron which show 60% homology at the amino acid level (Dubocovich et al., 2003). There are alternatively spliced isoforms of *MT* genes whose functions remain to be defined (Slominski et al., 2003a, Slominski et al., 2005a). It was shown that different genetic variants of *MT2* can affect body glucose homeostasis

(Bouatia-Naji et al., 2009, Prokopenko et al., 2009). Both receptors belong to the family of seven transmembrane receptors coupled to G proteins, i.e. either Gi or Gq/11 - depending on the receptor type (Dubocovich et al., 2003, Dubocovich et al., 2010). Melatonin activates its receptors at nanomolar or lower concentrations. Binding of melatonin to its receptors affects many cellular signaling pathways. The inhibition of cAMP and cGMP production is followed by the inhibition of CREB, PKA and c-FOS activities, inhibition of calcium and potassium signaling, modification of protein kinase C activity, stimulation of arachidonic acid release and modification of inositol phosphate turnover, phosphorylation of the mitogen-activated protein and extracellular signal-regulated kinases 1 and 2 (MEK1 and MEK2) as well as c-Jun N-terminal kinase (JNK) (Capsoni et al., 1994, Dubocovich et al., 2003, Dubocovich et al., 2010).

The oligomerization and dimerization of MT1 and MT2 receptors appear to play a role in the regulation of cell activity (Ayoub et al., 2002, Jockers et al., 2008, Maurice et al., 2010). In addition, melatonin-related receptor (MRR or GPR50), which has high protein sequence homology with MT1 and MT2, may form heterodimers with MT1 (Ayoub et al., 2002, Jockers et al., 2008). Retinoic acid orphan receptor type α (RORα) was proposed to serve as a putative melatonin nuclear receptor (Carlberg et al., 1994, Wiesenberg et al., 1998). However, crystallographic studies have shown that RORα is in fact a cholesterol sulphate, and not melatonin, receptor (Kallen et al., 2004). Accordingly, others have shown that after binding to MT1 melatonin can indirectly regulate phenotypic activity of RORα (Hill et al., 2009). It has to be noted that there are at least 4 splicing variants of this nuclear receptor, i.e. *RORα1, RORα2, RORα3, RZRα* (*RORα4*) (Becker-Andre et al., 1994, Carlberg et al., 1994, Pozo et al., 2004).

Melatonin exerts also receptor-independent activities. These include broad-spectrum direct antioxidant activity or indirect actions resulting from the activation of anti-oxidative and cytoprotective pathways, a property shared by AFMK and other melatonin metabolites (Hardeland et al., 2009, Reiter et al., 2007, Tan et al., 2001). These properties define melatonin and its metabolites as anti-apoptotic and anti-mutagenic agents (Fischer et al., 2008b, Hardeland et al., 2011, Reiter et al., 2007, Slominski et al., 2008a). Melatonin can also regulate cell metabolism by acting on mitochondria (Hardeland et al., 2011, Semak et al., 2005). Some receptor-independent melatonin actions may be partly mediated via the cytosolic flavoprotein quinone reductase II (NQO2), which is involved in cellular resistance to oxidative stress and detoxification and possesses a melatonin-binding site (previously proposed as a melatonin receptor type 3 (MT3) (Jockers et al., 2008, Nosjean et al., 2000). Melatonin metabolites, including AFMK, and AMK, generated by UVB or oxidative stress can be stronger antioxidants than melatonin itself (Fischer et al., 2006a, Hardeland et al., 2007, Seever and Hardeland, 2008). These receptor-independent protective actions of melatonin and its metabolites would require high intracellular levels of the molecules, which can only be met by melatonin in situ production in the relevant tissue, since cellular melatonin uptake is very limited because only 0.1% of extracellular melatonin can enter the cell (Fischer et al., 2006a).

3.4. Melatonin receptors in the skin

The major compartments of the skin, ie. the epidermis, dermis and adnexa, are targets for melatonin regulation (Fischer et al., 2008a, Slominski et al., 2005a, Slominski et al., 2008a). More specifically, melatonin was implicated in the regulation of hair growth cycle (Fischer et al., 2008a, Kobayashi et al., 2005, Slominski et al., 2005c), cutaneous pigmentation (Slominski et al., 2004e) as well as skin physiology and pathology (Slominski et al., 2005a) including melanoma (Fischer et al., 2006c, Slominski and Pruski, 1993, Yu and Reiter, 1993) and vitiligo (Schallreuter et al., 2008a, Slominski et al., 1989). Since those actions have been recently discussed (Dubocovich et al., 2010) the description below will be short.

The field of hair growth was the subject of an intensive research in Australia and New Zealand, where experiments on fur-covered animals revealed that melatonin stimulates hair growth. For instance, melatonin-supplemented diet increased the rate of hair growth in a springtime (Welch et al., 1990). The results were confirmed in other experimental models (Ibraheem et al., 1994, Nixon et al., 1993). It is likely that fur growth is mediated by melatonin-binding sites/receptors, since these are expressed in rodent skin (Kobayashi et al., 2005, Slominski et al., 1994, Slominski et al., 2004b). Clinical studies in women suffering from androgenic alopecia showed a positive effect of melatonin on human hair growth, suggesting it as a potential hair growth regulator in humans (Fischer et al., 2004).

Expression of cell surface MT receptors in the skin varies in different species. To illustrate, skin from the C57BL/6 mouse expresses the *MT2* gene predominantly (Kobayashi et al., 2005) or exclusively (Slominski et al., 2004b), while human skin expresses both MT receptors although a bias towards *MT1* gene expression was observed. The MT1 represents the predominant form of melatonin receptor found in both whole skin and cultured cells (Slominski et al., 2005a, Slominski et al., 2003a). As shown by immunocytochemical studies the expression of MT1 and MT2 proteins in human skin was cell type- and cell compartment-dependent (Slominski et al., 2005a), which suggests that the selectivity of melatonin action could be achieved by spatial compartmentalization and the specificity of signal transduction pathways. The expression of MT receptors was modified by environmental factors in a cell type-specific fashion (Slominski et al., 2005a, Slominski et al., 2003c). For example, UVB at 100 mJ/cm^2 induced expression of the *MT1* gene in neonatal epidermal melanocytes, and down-regulated it in melanoma cells. *MT1* gene expression was also dependent on the donor, e.g. in some samples of dermal fibroblasts it was not detectable (Slominski et al., 2005a, Slominski et al., 2003c). *MT2* gene expression was also upregulated or modified by UVB in epidermal keratinocytes (normal and immortalized), epidermal melanocytes and dermal fibroblasts. UVB also induced alternatively spliced *MT2b* isoform in epidermal melanocytes, keratinocytes and dermal fibroblasts (Slominski et al., 2003a). *MT2b* isoforms have two open reading frames (*orf*) encoding the putative proteins. The first *orf*, called MT2b1, would generate a truncated protein of 79 amino acids containing the N-terminal and first transmembrane sequence followed by 8 amino acids of MT2 with the sequence GEHHS added due to a frame shift and the addition of a stop codon. The second *orf*, MT2b2, if translated, would code a protein of 247 amino acid protein, lacking the TM 1-3 domains (Slominski et al., 2003a, Slominski et al., 2005c).

Concerning *RORα* nuclear receptor gene, all of the tested human skin cell types (keratinocyte, melanocyte and fibroblast lineages) expressed at least one of the three *RORα* isoforms except for *RORα3* gene (Fischer et al., 2006c, Slominski et al., 2005a). Furthermore, UVB down-regulated the expression of *RORα* in HaCaT keratinocytes and upregulated it in normal neonatal melanocytes. *RORα1* and *RORα2* expression was detected only in dermal fibroblasts and in immortalized melanocytes (*RORα2* only) while being undetectable in normal epidermal melanocytes and in keratinocytes (Slominski et al., 2005a). It is likely that *RORα* gene, due to the alternative splicing (the gene contains 23 exons within a genomic region that spans 732,840 bp), codes other isoforms, as we detected additional DNA fragments of an unexpected length using standard *RORα1* and *RORα2* primers (Slominski et al., 2005a). The hair cycle dependent expression of RORα was detected in mouse skin (Kobayashi et al., 2005). The current challenge is to define whether the RORs still can serve as low affinity receptors for melatonin taking into consideration that RORα is a specific receptor for sterols (Kallen et al., 2004) and that its role as a receptor for melatonin was questioned (Dai et al., 2001).

3.5. Melatonin protects against skin damage

Serving as an antioxidant and radical scavenger (Tan et al., 2002), melatonin acts as a protecting factor against UVR-induced damage in the skin (reviewed by Fischer et al., 2008b, Slominski et al., 2005a, 2008a). In fact, melatonin is able to prevent sun-damage but only when it is administered prior to the UVR exposure and/or is present at the irradiation site (Bangha et al., 1996, Bangha et al., 1997, Dreher et al., 1999, Dreher et al., 1998). In vitro, melatonin increased cell viability in UV-irradiated fibroblasts (Lee et al., 2003), and decreased apoptosis (Ryoo et al., 2001). Melatonin also protected human leukocytes against UV-induced damage, significantly suppressing ROS formation. It had even stronger radical-scavenging properties than vitamin C and Trolox (Fischer et al., 2002). In human epidermal keratinocytes melatonin protected against UV-induced reduction of cell viability (Fischer et al., 2006b, Fischer et al., 2008c). This effect was found to be receptor-independent (it required high doses of melatonin), and involved anti-apoptotic activities. The interactions between pathways stimulated by UVB and melatonin may be complex since melatonin also attenuated the expression of several genes whose expression was known to be up-regulated by UVB (Pisarchik et al., 2004). Thus, melatonin could have a clinically relevant protective action against UVR when used as a sun protective cream component. Although melatonin photo-stability is a limiting factor, its metabolites 6-hydroxymelatonin and N1-acetyl-N2-formyl-5-methoxykynurenamine can retain significant anti-oxidant activity (Maharaj et al., 2002). A challenging question is whether protective functions of melatonin depend partly on its regulation of NQO2 function, since NQO2 gene expression is ubiquitous in skin cells (Slominski et al., 2005a).

3.6. Conclusions

Melatonin is generated and metabolized in the skin to affect its phenotype as well as to serve as a protective agent against UV radiation. Some of the melatonin effects are mediated through its interaction with melatonin receptors. Other actions result from direct, receptor-independent effects of this free radical-scavenging molecule as well as metabolic and protective effects induced by melatonin or its metabolites. The pleiotropic activities of the cutaneous melatoninergic system are mediated by cell-specific intra-, auto- or paracrine mechanisms, allowing a counteraction or attenuation of both environmental and endogenous stressors leading to the maintenance of skin integrity, and perhaps affecting body's homeostasis (Fig. 9). Local melatoninergic systems could also modify the activities of the cutaneous neuroendocrine network and influence global homeostasis as shown at Figures 1 and 2.

4. CUTANEOUS CHOLINERGIC SYSTEM

Acetylcholine acts via nicotinic or muscarinic receptors. There are several subtypes of nicotinic receptors that are built of pentamers of at least seventeen (α1–α10, β1–β4, γ, δ, ε) subunits (Wu and Lukas, 2011). Several subunits of the same type may be present in any given receptor type (e.g. α1 and α5). Nicotinic receptors signal by forming ligand-regulated cation channels. There are five subtypes of muscarinic receptors (M1-M5) that act through G protein-coupled signaling (Graef et al., 2011). Acetylcholine is synthesized by choline acetyltransferase from acetyl coenzyme A and choline. Acetylcholinesterase degrades acetylcholine to acetate and choline. Human keratinocytes synthesize, secrete, and degrade acetylcholine. Choline acetyltransferase is present in all layers of human epidermis while acetylcholinesterase is present only in basal keratinocytes (Grando et al., 1993). The role of cholinergic system in the skin has been reviewed extensively by Grando and coworkers (Grando et al., 2006). The role of acetylcholine-cholinergic receptor system in the skin, which among others regulates the function of eccrine glands, is well-known (Fitzpatrick et al., 1993). However, the exclusive role of muscarinic system in sweat glands was challenged

by finding nicotinic receptors in myoepithelial and acinar cells of those glands (Kurzen and Schallreuter, 2004).

Human keratinocytes express the α3, α5, α7, α10, β1, β2, and β4 nicotinic receptor subunits and all types of muscarinic receptors (Grando, 1997, Grando, 2006, Grando et al., 1996, Grando et al., 2006, Grando et al., 1995). The expression of those receptors changes during the process of keratinocyte differentiation. Basal keratinocytes respond to acetylocholine predominantly via nicotinic receptor α3β2(β4) with or without α5 subunit and the M2 and M3 muscarinic receptors. Keratinocytes of the prickle layer have more α5-containing α3-nicotinic receptors, and also express α9-nicotinic as well as M4- and M5-muscarinic receptors. α7-nicotinic and M1-muscarinic receptors are mainly found on keratinocytes of the granular layer of epidermis (Grando et al., 2006). The α7 nicotinic receptor has the most prominent role in keratinocyte differentiation since its deactivation leads to the apoptosis of keratinocytes and the inhibition of their differentiation. The α3β2 receptor regulates chemokinesis of leukocytes (Arredondo et al., 2002, Chernyavsky et al., 2004a), while the activation of nicotinic receptors stimulates keratinocyte motility, with α9 subtype of nicotinic receptor being the most significant in this respect (Nguyen et al., 2000). It was suggested, that, acting simultaneously, nicotinic (primarily α7) and muscarinic (primarily M1) receptors are responsible for directional migration of keratinocytes via the Ras/Raf-1/MEK1/ERK pathway (Chernyavsky et al., 2004a, Grando et al., 2006). Also, the activation of M3 muscarinic receptors favors the expression of migratory integrins and that of M4 promotes sedentary integrins, thereby further solidifying a pivotal role of the cholinergic system in keratinocyte migration and wound re-epithelialization (Chernyavsky et al., 2004b). Muscarinic receptors' activation increased relative amounts of Ki-67, PCNA and p53 mRNAs as well as PCNA, cyclin D1, p21 and p53 proteins affecting cell cycle (Arredondo et al., 2003).

Acetylcholine's potential role in the pathogenesis of pemphigus can be demonstrated by the fact that cholinergic receptors' activation on keratinocytes altered the expression of desmoglein 1, desmoglein 3 and the phosphorylation status of desmoglein 3 (Nguyen et al., 2003). Cholinergic agonists inhibit the antibody-induced acantholysis and adhesion molecules' phosphorylation in pemphigus vulgaris. M1 ligand binding leads to the activation of both serine/threonine and tyrosine phosphatases, whereas binding of a ligand to the α7 nicotinic receptor activates the tyrosine phosphatase and inhibits Src (v-src sarcoma (Schmidt-Ruppin A-2) viral oncogene homologue). These processes lead to the dephosphorylation of adhesion molecules and, thus, the inhibition of acantholysis (Chernyavsky et al., 2008).

SLURP family proteins regulate the function of the cholinergic system and their abnormalities are found in one of the palmoplantar keratodermas (Mal de Meleda) and psoriasis (Fischer et al., 2001, Tsuji et al., 2003). Local acetylcholine levels are increased in atopic dermatitis (Wessler et al., 2003).

Human melanocytes express the M_1–M_5 subtypes of muscarinic receptors and α1, α3, α5, α7, β1, β2, γ, and Δ subunits of nicotinic receptors (Buchli et al., 2001). Acetylcholine induces pigmentation via nicotine receptors and inhibits it via M2 and M4 muscarinic receptors (Grando et al., 2006, Kurzen and Schallreuter, 2004, Wallstrom et al., 1999). The activity of acetylcholine esterase is decreased in vitiligo (Iyengar, 1989). The M4 muscarinic receptor may have a pivotal role in the regulation of murine hair pigmentation (Hasse et al., 2007).

All the elements of the cholinergic system are expressed in Langerhans cells and lymphocytes. Muscarinic M3 receptor expression on lymphocytes is much stronger than other receptor subtypes (Tayebati et al., 2002).

4.1. Conclusions

The cholinergic system plays a pivotal role in the regulation of keratinocytes' homeostasis. Their differentiation, motility, adhesion and cell cycle are modified by acetylcholine. The differential expression of the receptors has been documented in detail. The α7 nicotinic receptor plays a key role in keratinocyte differentiation and α9 nicotinic, M3 and M4 muscarinic receptors in keratinocyte migration. In the melanocytes the activation of nicotinic receptors induces pigmentation, while the opposite is true for M2 and M4 muscarinic receptors. The cholinergic system is implicated in such skin pathologies as palmoplantar keratoderma (Mal de Meleda type), psoriasis, atopic dermatitis, vitiligo and pemphigus. In addition, communication between the cutaneous neuroendocrine system and the rest of the body is partly achieved via the cholinergic system (Figs. 1, 2).

5. CORTICOTROPIN (CRF) SIGNALING SYSTEM IN THE SKIN

5. 1. CRF and urocortins

Corticotrophin-Releasing Factor (CRF), a 41 amino acid long hypothalamic neuropeptide, discovered by Vale and Rivier (Spiess et al., 1981, Vale et al., 1981) together with related urocortin (Urc1-3) are brain neuropeptides that regulate behavioral, autonomic, endocrine, reproductive, metabolic and immune functions (Grammatopoulos and Chrousos, 2002, Hillhouse et al., 2002, Perrin and Vale, 1999). In peripheral tissues they act as local immunomodulators with predominantly proinflammatory actions (Hasse et al., 2007, Slominski, 2003b, Slominski et al., 2006c, Theoharides and Cochrane, 2004) as well as they directly regulate cardiovascular, gastrointestinal, reproductive and gestational activities (Hillhouse and Grammatopoulos, 2006a). These neuropeptides exert their regulatory activities via interaction with CRF receptors, CRF1 and CRF2, which were cloned and initially characterized by Vale's group and others (Grammatopoulos and Chrousos, 2002, Hillhouse and Grammatopoulos, 2006b, Hillhouse et al., 2002, Perrin and Vale, 1999, Slominski et al., 2001).

5.2. Expression and functions of CRF and urocortins in the skin

The CRF signaling system regulates human skin homeostasis (Janjetovic et al., 2009, Slominski and Wortsman, 2000, Slominski et al., 2000c, Slominski et al., 2006c, Zmijewski and Slominski, 2009b, Zmijewski and Slominski, 2010a) (Fig. 10). In fact, we were the first to detect CRF and Urc1 production in the skin (Roloff et al., 1998, Slominski et al., 1996a, Slominski et al., 1998b, Slominski et al., 2000b, Slominski et al., 2000c, Slominski et al., 1999c), which was stimulated by UVR and cAMP, and was inhibited by dexamethasone (Slominski et al., 1996a, Slominski et al., 1998b). We also identified and characterized the CRF receptors in the skin and defined their functional activity (Slominski et al., 2000c, Slominski et al., 2001, Slominski et al., 2006c, Slominski et al., 1999c), findings confirmed and extended by others. CRF and urocortins can inhibit proliferation of cultured human keratinocytes and melanocytes (Quevedo et al., 2001, Slominski et al., 2000b, Slominski et al., 2006a, Zbytek et al., 2005). They also stimulate cell differentiation (Zbytek et al., 2005) and modulate the expression of cell surface adhesion molecules and cytokine production by human keratinocytes (Quevedo et al., 2001, Zbytek et al., 2002). CRF and related peptides stimulate POMC expression and corticosterone and cortisol production (Cirillo and Prime, 2011b, Hannen et al., 2011, Ito et al., 2005, Rousseau et al., 2007, Skobowiat et al., 2011, Slominski et al., 2006c, Slominski et al., 2005d, Slominski et al., 2005e, Vukelic et al., 2011, Zbytek et al., 2006b). These phenotypic effects of CRF in the skin are mediated by

interaction with CRF1, which is the predominant receptor type expressed in human epidermis, and CRF2, and appear to be secondary to the modulation of intracellular concentrations of cAMP, IP3, Ca^{2+} or NF-κB activity (Fazal et al., 1998, Slominski et al., 2006a, Slominski et al., 2005e, Slominski et al., 1999c, Wiesner et al., 2003). Moreover, CRF also stimulates steroidogenic activities in sebocytes which express both CRF1 and CRF2 (Zouboulis et al., 2002). Thus, CRF and Urc exhibit non-endocrine activities like regulation of cell proliferation, differentiation and immune cell interactions, thereby defining these peptides as a novel type of growth factors/pleiotropic cytokines (Kauser et al., 2006, Slominski et al., 2006a, Slominski et al., 2006c, Zbytek et al., 2006a, Zbytek and Slominski, 2007).

These pleiotropic activities of CRF and urocortins give the mechanism of regulating CRF signaling in the skin a significant priority (Slominski et al., 2006c, Slominski et al., 1999c, Zmijewski and Slominski, 2010a). CRF1 is expressed in all major cellular lineages of the skin, while CRF1α prevails in human epidermis, and CRF2 is expressed in all mouse cutaneous compartments (Slominski et al., 2004a, Slominski et al., 2001, Slominski et al., 2006c). A major challenge in this area is the functional implication of the coupling of different CRF1 isoforms to different signal transduction systems (Fig. 11, 12) (Janjetovic et al., 2009, Pisarchik and Slominski, 2004b, Pisarchik and Slominski, 2001, Slominski et al., 2004a, Slominski et al., 2001, Slominski et al., 2006a, Slominski et al., 2006c, Zmijewski and Slominski, 2009a, Zmijewski and Slominski, 2009b, Zmijewski and Slominski, 2010). This differential coupling could provide the mechanistic explanation for observed organ- and cell type-dependent variability in the phenotypic response to CRF as previously suggested (Pisarchik and Slominski, 2004b, Pisarchik and Slominski, 2001, Slominski et al., 2004a, Slominski et al., 2006c, Zmijewski and Slominski, 2010a).

5.3. Splicing of CRF receptor transcripts

Alternative splicing of mRNA is one of the most important mechanisms accountable for genomic variability in higher eukaryotes (Luco et al., 2011). Therefore most human genes, including those coding for G protein-coupled receptors (GPCRs), are sources for multiple protein isoforms.

CRF receptors are members of class B (secretin family) of G protein-coupled receptors (GPCRs) and are closely related to calcitonin, growth-hormone-releasing hormone (GHRH), glucagon, glucagon-like peptides, parathyroid hormone (PTH), pituitary adenylate-cyclaseactivating peptide (PACAP) and secretin receptors (Lagerstrom and Schioth, 2008). Members of the class B of the GPCR receptor family bind to peptides longer than 27 amino acid residues and are expressed in the majority of endocrine and non-endocrine cells (Hillhouse and Grammatopoulos, 2006a, Perrin and Vale, 1999, Slominski and Wortsman, 2000).

In humans, the *CRF1* gene, which contains 14 coding exons was mapped to chromosome 17 (17q12-q22) (Polymeropoulos et al., 1995). CRF2 gene has 15 exons (Hillhouse and Grammatopoulos, 2006a, Slominski et al., 2001) and is located on chromosome 7 (7p14.3). The coding sequences of the two receptors show high degree of homology, although not uniformly distributed along the sequence. A comparison of the protein sequences revealed three distinct regions of homology, corresponding to the structural domains of CRF receptors. Extracellular domain (ECD) of the CRF receptor is responsible for substrate recognition and binding, and this region showed the lowest homology (40%) between CRF1 and CRF2. This feature most probably reflects differential affinity to ligands (CRF and Urc 1-3) (Hillhouse and Grammatopoulos, 2006a). On the other hand, 7TM domain and intracellular and extracellular loops are highly conserved with homology of around 80%. The most conserved part of the CRF receptor is the third intracellular loop involved in the

interaction with G-proteins (Hemley et al., 2007, Hillhouse et al., 2002). Despite a high level of similarity the pattern of splicing variants of the two known CRF receptor genes (*CRF1 and CRF2*) seems to be unique for each pre-mRNA (Fig. 11).

5.3.1. CRF1 mRNA splicing variants—Processing of pre-mRNAs encoding *CRF* receptors may result in an alternative splicing with at least ten variants of *CRF1* mRNA (α, β, c, d, e, f, g, h and i) (Hillhouse and Grammatopoulos, 2006a, Karteris et al., 2011, Pisarchik and Slominski, 2002, Pisarchik and Slominski, 2001, Slominski et al., 2007a, Slominski et al., 2006c, Zmijewski and Slominski, 2010). Importantly, all of those isoforms except newly discovered *CRF1β/d* and *CRF1i* were found in human skin (Mikhailova et al., 2007, Slominski et al., 2007a, Zmijewski and Slominski, 2010, Zmijewski and Slominski, 2011). Interestingly, only one isoform of *CRF1* (CRF1β) contains all 14 exons, while the main functional isoform, CRF1α, has an exon 6 spliced out. The exon 6 seems to be unique for CRF1β, although a recent study by Karteris and coworkers (2011) revealed a new isoform, named CRF1β/d since it shared the properties of isoform CRF1β (exon 6) and CRF1d (lack of exon 13). This finding raises a theoretical possibility of the expression of all *CRF1* splicing variants with and without exon 6. Other *CRF1* isoforms might be divided into three groups: soluble receptors (CRF1e and CRFh), receptors with defects in the extracellular domain (ECD) (isoform c) and receptors with impaired 7TM domain (CRF1d, f, g and also CRF1β/d fits to this group). The detailed exonal organization of CRF1 isoforms is shown in Figure 11 and was discussed elsewhere (Hillhouse and Grammatopoulos, 2006a, Slominski et al., 2006c, Zmijewski and Slominski, 2010b, Zmijewski and Slominski, 2011). It has to be noted that alterative splicing of *CRF1* also results in a frame shift which introduces premature stop codon to the sequence of CR1e, f, g and h. Alternative splicing of CRF1 receptor mRNA seems to be a conserved phenomenon in evolution because CRF1 isoforms were also identified in rat (Hillhouse and Grammatopoulos, 2006a, Slominski et al., 2001), mouse (Pisarchik and Slominski, 2001) and hamster (Pisarchik and Slominski, 2002). Also some splice variants are conserved among the members of the family B of GPCRs. For instance, characteristic deletion of exon 13 was found in *CRF1* isoform d and calcitonin receptor (Grammatopoulos et al., 1999, Markovic et al., 2008, Seck et al., 2005, Zmijewski and Slominski, 2009b). Theoretically, it is possible that, due to the alternative splicing, also “headless” CRF1 receptor isoforms could be coded by CRF1 pre-mRNA (Slominski et al., 2006c). Their presence was predicted based on the known mRNA sequences of isoforms CRF1e and h (Pisarchik and Slominski, 2001, Zmijewski and Slominski, 2010a). The mRNAs of those isoforms - due to the presence of the alternative code premature stop codon and alternative ATG start cordons - could theoretically allow for the synthesis of “headless” isoforms of CRF1 receptor. Such ECD domain-missing isoforms were identified for the closely related calcitonin receptor (Nag et al., 2007). However, proof for the existence of CRF1 “headless” isoforms remains to be provided.

5.3.2. CRF2 splicing variants—In theory, *CRF2* gene has a capacity for similar number of isoforms as shown for CRF1 (http://www.ncbi.nlm.nih.gov/IEB/Research/Acembly/), although only CRF2α, β, γ and soluble sCRF2 isoforms of *CRF2* were well characterized (Grammatopoulos and Chrousos, 2002, Hillhouse et al., 2002). In contrast to *CRF1* gene, the gene of *CRF2* receptor has at least three alternative starting codons coded by alternative exons located on 5′-end of the *CRHR2* gene (see Fig. 11). In addition, the presence of the soluble isoform of *CRF2* (sCRFR2α) was also reported in mouse brain (Perrin et al., 2003) and headless isoform of *CRF2* was found in stomach (GenBank accession No. E12750; Patent: JP199707289-A).

5.3.3. Expression of CRF1 and CRF2 isoforms in the skin—In human skin, *CRF1* gene is expressed in both epidermal and dermal compartments whereas *CRF2* is detected

predominantly in adnexal structures such as hair follicles (Kauser et al., 2006, Slominski et al., 2004a) or sebaceous glands (Kauser et al., 2006). It seems that this pattern is characteristic for humans because mouse skin expresses both *CRF1* and *CRF2* (Slominski et al., 2004a, Slominski et al., 2007a), and both of them take part in the regulation of skin physiology (Kauser et al., 2006, Slominski et al., 2006c, Slominski et al., 2004a).

All studied human epidermal and dermal cell lines express the main CRF1 isoform α and for some cells like adult epidermal keratinocytes and melanocytes, it is the only isoform found under normal conditions (Pisarchik and Slominski, 2001, Slominski et al., 2001). Also melanocytes, keratinocytes and fibroblasts found in hair follicles express CRF1α (besides the previously mentioned CRF2) (Kauser et al., 2006, Slominski et al., 2006c, Slominski et al., 2004a). However, neonatal epidermal keratinocytes, dermal fibroblasts and several melanoma cell lines express multiple CRF1 variants (Pisarchik and Slominski, 2001, Slominski et al., 2004a).

5.3.4. Modulation of the expression of CRF1 isoforms and its physiological relevance—Although the regulation of the alternative splicing of CRF receptor genes' remains unknown, a theoretical model of alternative splicing with a potential involvement of U1 and U2 small nuclear ribonucleoproteins (snRNPs), splicing activators and Ser/Thr kinases was proposed (Markovic and Grammatopoulos, 2009). Here we will discuss only biological factors which affect *CRF* receptor splicing with relevance to human skin.

The *CRF1* expression pattern and alternative splicing is regulated by diverse physiological and pathological factors, including cell growth conditions or exposure to the ultraviolet irradiation (Zmijewski and Slominski, 2010b). In human immortalized HaCaT keratinocytes CRF1α is the only isoform expressed in confluent culture. However, fast growing (subconfluent) cells express multiple isoforms including α, c and e (Zmijewski and Slominski, 2009b). In addition, the expression of CRF1 mRNA and protein increases with confluence of HaCaT keratinocyte cultures (Zmijewski and Slominski, 2009b). The above phenomena may also explain differences in the CRF1 expression between neonatal and adult epidermal keratinocytes (Slominski et al., 2004a, Slominski et al., 2007a).

The pathological conditions can influence the expression of CRF1 receptor as shown in skin biopsies from psoriatic patients (Tagen et al., 2007, Zmijewski and Slominski, 2009b). It is worth mentioning that most of the studied melanomas expressed multiple CRF1 isoforms including CRF1α, except for SKMEL-188 melanoma cells that exclusively expressed CRF1d (Pisarchik and Slominski, 2001, Slominski et al., 2004a). This raises a question whether CRF1 splicing is involved in the pathogenesis of skin hyperproliferative (malignant or bening) and inflammatory diseases and whether external and internal stressors can affect skin physiology through context-dependent *CRF1* alternative splicing leading to the differential CRF signaling in this organ (Slominski, 2009b, Slominski et al., 2006c, Zmijewski and Slominski, 2010).

A single-nucleotide polymorphism (SNP) of *CRF1* gene might be an additional factor with high impact on *CRF1* expression and splicing. There is a growing body of evidence that SNPs of *CRF1* are associated with several human pathologies including hypertension, abusive behavior and depression (Kamdem et al., 2008, Schmid et al., 2009, Wasserman et al., 2008). Therefore, it is possible that SNPs might influence the *CRF1* gene expression and/or splicing of its premRNA.

Recent studies revealed a potential mechanism and significance of CRF1 isoforms' expression in the epidermal and dermal cell lines and other models (Jin et al., 2007, Karteris et al., 2011, Markovic et al., 2008, Pisarchik and Slominski, 2002, Pisarchik and Slominski,

2001, Slominski et al., 2007a, Slominski et al., 2006a, Slominski et al., 2006c, Sztainberg et al., 2009, Zmijewski et al., 2007, Zmijewski and Slominski, 2009b). As stated above, the pattern of CRF1 isoform expression depends on cell type and culture growth condition. These data also correlate with the observed changes in the responsiveness to CRF or urocortin. The current model of the regulation of CRF-signaling confirms the central role of CRF1α and suggests at least modulatory roles for the other CRF1 isoforms in signal transduction (Fig. 12) (Zmijewski and Slominski, 2010). For example, alternative splicing may decrease the levels of CRF1α transcripts. Isoform CRF1e is a good candidate. This isoform consists of only has first coding exons followed by the premature termination codon in exon 5, resulting in a frame shift due to the removal of exons 3 and 4. This isoform could be subjected to fast decay mechanisms. An additional mechanism of the regulation of CRF1 function by the expression of multiple splicing variants may include heterooligomerization of CRF1 isoforms leading to changes in CRF1α trafficking to the cell membrane, its localization and function. Oligomerization of GPCR is a wellknown mechanism of the regulation and activation of the GPCR A family. Interestingly, oligomerization of CRF1 isoforms was found in different cell compartments of HaCaT epidermal keratinocytes (Zmijewski and Slominski, 2009a) and also in pituitary AtT-20 cells (Zmijewski and Slominski, 2009b). These findings confirmed earlier studies which showed dimerization of CRF1α (Kraetke et al., 2005) and heterodimerization of CRF1 with vasopressin V1b receptor (Young et al., 2007). Thus, the co-expression of CRF1α with CRF isoforms defective in 7TM domain (d, f, g) may result in the retention of heterodimers inside the cells, and thus inhibition of the translocation of the newly synthesized CRF1α receptors to the cell membrane. Based on structural modeling of CRF1 isoforms, it was concluded that alterations to the sequence caused by alternative splicing should result in the instability of receptors in the cell membrane (Slominski et al., 2006c). Indeed, CRF1d, when overexpressed in HaCaT keratinocytes, localized predominantly to the endoplasmic reticulum, and CRF1f and CRF1g co-localized within Golgi cisterns. Thus, none of the CRF1 isoforms with impaired 7TM domain showed proper membrane localization (Zmijewski and Slominski, 2009a, b). The overexpression of those isoforms can influence downstream signaling including cAMP, IP_3 production, and calcium mobilization, followed by altered transcriptional activity (Grammatopoulos and Chrousos, 2002, Grammatopoulos et al., 1999, Hillhouse and Grammatopoulos, 2006a, Markovic et al., 2008, Pisarchik and Slominski, 2004b, Slominski et al., 2006a, Slominski et al., 2007b, Wietfeld et al., 2004, Zmijewski et al., 2007, Zmijewski and Slominski, 2009a, Zmijewski and Slominski, 2009b, Zmijewski and Slominski, 2010). The third mechanism of the regulation of CRF signaling may involve direct alterations of the receptor function. CRF1d, f, g isoforms and their heterodimers with CRF1α, found predominantly inside the cell, could not be activated by extracellular ligands (Pisarchik and Slominski, 2004a, Slominski et al., 2007b, Zmijewski and Slominski, 2009a, Zmijewski and Slominski, 2009a, b, Zmijewski and Slominski, 2010). Even if isoforms with impaired 7TM domains (CRF1d, f, and g) would reach proper cell membrane localization, the downstream signaling would be impaired due to improper binding/activation of G-protein (Zmijewski and Slominski, 2009b, Zmijewski and Slominski, 2009b, Zmijewski and Slominski, 2010a). On the other hand, the isoform CRF1c, despite its proper membrane localization (Slominski et al., 2006c, Zmijewski and Slominski, 2009a, Zmijewski and Slominski, 2009b) has a deletion of exon 3 encoding the main part of receptor's extracellular domain, which resulted in impaired ligand binding (Slominski et al., 2006c, Zmijewski and Slominski, 2009a). Indeed, CRF1 expressed in COS-1 cells failed to bind antagonist ([I^{125}]oCFR (Ross et al., 1994). An increase in cAMP production was only observed after stimulation with high concentration of human CRF indicating attenuation of signaling by CRF1c in comparison to CRFα (Karteris et al., 1998).

A fourth type of the CRF signaling modulation is represented by the soluble CRF1h isoform (Slominski et al., 2006c, Zmijewski and Slominski, 2011). The intracellular retention and

co-localization within ER of CRF1h was shown in cells overexpressing this isoform (Zmijewski and Slominski, 2009a, Zmijewski and Slominski, 2009b). In addition, CRF1h was released from the cells to the media and inhibited CRF signaling (Pisarchik and Slominski, 2004b, Zmijewski and Slominski, 2009b). If this process occurs in vivo, it would be consistent with a well-known mechanism of action of soluble receptors (also called decoy receptors) and similar to the function of CRF2 soluble isoform (sCRF2) (Chen et al., 2002). The described models of the CRF signaling regulation via the expression of CRF1 isoforms may be not unique to skin cells but can represent a global mechanism valid for other tissues and cell lineages, because many organs and tissues express multiple CRF1 isoforms (Fig. 13).

5.3.5. Conclusion—CRF, urocortins and CRF receptors are widely expressed in human skin. The phenotype of skin cells is affected by endogenously produced CRF and urocortins via a variety of signal transduction systems. Furthermore, expression of multiple CRF1 isoforms may represent additional means of regulating CRF-mediated stress responses at different levels (Fig. 11). Different stress signals were found to influence *CRF1* splicing and signaling but there are also indications that other factors such as small nucleotide polymorphism may influence CRF signaling by modification of the CRF1 pre-mRNA splicing. The recently proposed mechanism of the CRF signaling regulation by its receptor splicing may explain the observed changes in cell responsiveness to CRF and CRF-like ligands (Fig. 12).

Modulation of *CRF1* splicing may have a direct impact on the differentiation and proliferation of various skin cell types. Alterations of *CRF1* splicing mechanism can ultimately lead to the development or aggravation of symptoms of several skin pathologies including acne, psoriasis or skin cancer (Fig. 10).

6. STEROIDOGENESIS IN THE SKIN

6. 1. An overview

Adrenocortical steroidogenesis is initiated by the interaction of ACTH with melanocortin receptor type 2 (MC2-R) that stimulates secretion and production of cortisol via the activation of steroidogenic enzymes and cholesterol mobilization or transport into mitochondria (Felig and Frohman, 2001, Payne and Hales, 2004). Prolonged ACTH effects include induction of corresponding enzymes, and the entire process is linked to the ACTH-stimulated cAMP production (Felig and Frohman, 2001, Payne and Hales, 2004). The biochemical pathway is initiated by the rate-limiting enzyme cytochrome P450scc (encoded by the *CYP11A1* gene) that cleaves cholesterol side chain to produce pregnenolone, precursor to all steroids (Payne and Hales, 2004, Tuckey, 2005). In a classical pathway, pregnenolone is further transformed to corticosterone or cortisol through sequential action of 3βHSD/isomerase, P450c17, P450c21 and P450c11β enzymes and then released into circulation (Felig and Frohman, 2001, Payne and Hales, 2004). Specifically, 3βHSD/isomerase transforms pregnenolone to progesterone, and 17(OH)pregnenolone to 17(OH)progesterone, P450c17 catalyzes 17α-hydroxylation of pregnenolone or progesterone to 17(OH)pregnenolone or 17(OH)progesterone, P450c21 hydroxylates progesterone to deoxycorticosterone (DOC) or 17(OH)progesterone to 11-deoxycortisol, while P450c11β hydroxylates DOC to corticosterone and 11-deoxycortisol to cortisol (Felig and Frohman, 2001, Payne and Hales, 2004, Simard et al., 2005). ACTH also stimulates production of mineralocorticoids and sex hormones via MC2-R and has a trophic effect on the adrenal cortex (Felig and Frohman, 2001) (Fig. 14). Low level production of cortisol via the classical pathway was reported in peripheral tissues (Taves et al., 2011) including the gastrointestinal tract, brain (Davies and MacKenzie, 2003; Do Rego et al., 2009), immune cells (Costa et al., 2009, Vacchio et al., 1994), and also in colon cancer (Sidler et al., 2011).

In addition, cortisol levels are also regulated by 11β-HSD1 (Draper and Stewart, 2005), which at high NADPH/$NADP^+$ ratios transforms cortisone to cortisol (Draper and Stewart, 2005, Tomlinson et al., 2004). Cortisol can also be transformed to cortisone by $NADP^{+\prime}$dependent enzyme 11β-HSD2 that acts exclusively as a dehydrogenase (Tomlinson et al., 2004). The expression of both 11β-HSD1 and 11β-HSD2 enzymes was shown in placenta, kidney, liver, fibroblasts and adipocytes (Bujalska et al., 1997, Bujalska et al., 2002, Ricketts et al., 1998, Tiganescu et al., 2011a).

6.2. Cutaneous corticosteroidogenic system

We were the first to demonstrate that human skin expresses genes encoding enzymes involved in the sequential metabolism of cholesterol to pregnenolone and to corticosteroids including cytochromes *P450scc*, *P450c17* and *P450c21*, and the *MC2-R* (receptor for ACTH) genes (Slominski et al., 1996d). These findings were later complemented by the demonstration of these enzymes' functional activity in epidermal and dermal skin cells (Rogoff et al., 2001, Slominski et al., 2000a, Slominski et al., 1999b, Slominski et al., 2002d, Slominski et al., 2004f) and that cutaneous steroidogenesis begins from cholesterol (Slominski et al., 2007a, Slominski et al., 2004d). Rapid metabolism of progesterone and deoxycorticosterone (DOC) was shown in rodent skin and cultured human normal and malignant skin (Slominski et al., 2000a, Slominski et al., 1999b, Slominski et al., 2002d). Thus, production of corticosterone and DOC-like steroid species was shown in rat skin (Slominski et al., 2000a). Also cultured malignant melanocytes showed progressive transformation of progesterone to DOC, 18-hydroxy-DOC and corticosterone, but not to aldosterone (Slominski et al., 1999a). Cortisol and corticosterone production was further documented in normal epidermal melanocytes (Slominski et al., 2005e) and dermal fibroblasts (Slominski et al., 2005d, Slominski et al., 2006b), with final evidence on cortisol synthesis by human skin cells provided by liquid chromatography-mass spectrometry (LC/MS) analysis (Slominski et al., 2005e, Slominski et al., 2006b). In agreement, cortisol production was demonstrated in human hair follicles (Ito et al., 2005, Sharpley et al., 2009), and cortisol production by epidermal and dermal skin cells was later confirmed by other authors (Cirillo and Prime, 2011a, Hannen et al., 2011, Vukelic et al., 2011). Interestingly, cutaneous cortisol production was mediated both by CYP11B1 and 11β-HSD1 activities (Cirillo and Prime, 2011a, Hannen et al., 2011, Slominski et al., 2007a, Tiganescu et al., 2011b, Vukelic et al., 2011). While some authors found cortisol production by early passages of human epidermal keratinocytes (Cirillo and Prime, 2011a, Hannen et al., 2011, Vukelic et al., 2011), we (Slominski et al., 2005e) and others (Milewich et al., 1986) did not detect cortisol in late passages of epidermal keratinocytes or melanocytes. In agreement with the last finding, in HaCaT keratinocytes, progesterone and DOC were metabolized rapidly to steroid products different from corticosterone, aldosterone and cortisol (Slominski et al., 2002d). These discrepancies may be due to the contamination of primary cultures of keratinocytes by other cell types (for example melanocytes) or differences in culture conditions. Cortisol production by skin cells was regulated by ACTH and factors raising cAMP level (Slominski et al., 2005e), IL-1 as well as by wound response (Vukelic et al., 2011) and high energy ultraviolet radiation (Skobowiat et al., 2011).

6.3. Production of sex hormones in the skin

The skin is an important organ transforming dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEA-S) or androstenedione, which predominantly originate from systemic circulation, to active sex hormones (Labrie et al., 2003, Ohnemus et al., 2006, Zouboulis, 2004, Zouboulis et al., 2007, Zouboulis and Degitz, 2004) (Fig. 14). In addition, in the skin local steroidogenic system (Ito et al., 2005, Slominski et al., 2002d, Slominski and Wortsman, 2000, Slominski et al., 2008b, Slominski et al., 2005d, Slominski et al., 2005e, Slominski et al., 2004d, Taves et al., 2011) produces 17(OH)pregnenolone and

17(OH)progesterone that are further metabolized to DHEA with their following metabolism to androgens and estrogens (Fig. 14), or other steroidal products (Slominski et al., 2009a, Slominski et al., 2002d, Slominski et al., 2009c).

DHEA of systemic or local origin is transformed by 3β-HSD into 4-androstenedione, and 5-androstene-3β,17β-diol into testosterone, while 17β-HSD converts DHEA into 5-androstene-3β,17β-diol, 4-androstenedione into testosterone, and androstanedione into DHT (Labrie et al., 2003, Labrie et al., 2000, Milewich et al., 1991, Simard et al., 1993, Zouboulis et al., 2008, Zouboulis and Degitz, 2004). Cutaneous testosterone is also converted into dihydrotestosterone (DHT) by the action of a 5α-reductase (reviewed by Zouboulis et al., 2008). Skin and subcutaneous adipose tissue is also an important site of estrogen production, in particular after menopause (Labrie et al., 2003, Ohnemus et al., 2006, Zouboulis et al., 2007). Furthermore, it is an important site of estrogen and androgens activation (Fig. 14) (Labrie et al., 2000, Ohnemus et al., 2006, Zouboulis et al., 2007, Zouboulis and Degitz, 2004). The locally produced sex hormones modify skin phenotype and function via interactions with the corresponding androgen and estrogen receptors (Labrie et al., 2003, Labrie et al., 2000, Ohnemus et al., 2006, Randall et al., 1993, Slominski and Wortsman, 2000, Zouboulis, 2004, Zouboulis et al., 2007, Zouboulis and Degitz, 2004).

6. 4. Conclusions

Mammalian skin is an extra-adrenal site of mineralo/glucocortidoid synthesis, which can be regulated by endogenous and environmental factors (Slominski et al., 2008c, Slominski et al., 2007a). Furthermore, the skin is an important site for estrogen and androgen production, activation or metabolism (Labrie et al., 2003, Ohnemus et al., 2006, Zouboulis et al., 2007). Interestingly, skin production of steroids seems to be cell type-dependent and subjected to the regulation by external factors such as ultraviolet radiation. These steroids act in intra-, auto or paracrine fashions to regulate local homeostasis. Moreover, skin and its subcutaneous tissue constitute an important source of estrogens and androgens in females, especially after menopause.

7. EQUIVALENT OF HYPOTHALAMO-PITUITARY ADRENAL AXIS (HPA) IN THE SKIN

7.1. Systemic HPA axis

The work of Hans Selye was fundamental in defining the hypothalamic-pituitary-adrenal (HPA) axis as the body's important coordinator of responses to systemic stress (Selye, 1936, Seyle, 1976). The HPA functional structure has been completed by determining that hypothalamic corticotropin releasing factor (CRF) acts as the regulator of the production of ACTH and β-endorphin in the anterior pituitary (Spiess et al., 1981, Vale et al., 1981). The HPA pathway (Fig. 15) is triggered by various stress factors which activate production of CRF in the paraventricular nucleus (PVN) (Chrousos, 1995, Chrousos and Gold, 1992, Owens and Nemeroff, 1991). In pituitary CRF binds to CRF type 1 receptors (CRF1) (Aguilera et al., 2001, Hillhouse and Grammatopoulos, 2006b, Perrin and Vale, 1999) increasing production and secretion of the proopiomelanocortin-derived (POMC) peptides, i.e. ACTH, MSH, and β-endorphin (Hillhouse and Grammatopoulos, 2006b, Pritchard and White, 2007, Smith and Funder, 1988). The arginine vasopressin (AVP) produced by the PVN can also act synergistically with CRF in activating the HPA axis (Chrousos, 1995, Itoi et al., 2004). In the adrenal cortex ACTH, by interacting with the MC2 receptors (MC2-R), stimulates production and secretion of cortisol in humans or corticosterone in rodents. These corticosteroids counteract the effects of stressors by mobilization of energy reserves, buffering tissue damages, and suppressing immune system. Moreover, corticosteroids via feed-back mechanisms inhibit the HPA axis through the suppression of CRF and POMC

production. The HPA axis is also controlled by cytokines, tissue modifiers and growth factors, which can be either produced in the brain or by peripheral tissues including cells of the immune system. Thus, there are various ways of controlling stress responses at the level of hypothalamus or pituitary that bypass the central brain coordinating centers (c.f. in Besedovsky and Rey, 2007, Blalock and Smith, 2007, Chesnokova and Melmed, 2002) (Figure 15).

7.2. HPA axis homologue is expressed in the skin

More than a decade ago we proposed that skin expresses a homologue of the HPA axis to regulate local stress responses (Slominski et al., 1996a). This concept was based on finding all molecular elements of the HPA axis in the mammalian skin, i.e. CRF, CRF1, POMC, ACTH, MC2R, glucocorticoid receptors and genes coding steroidogenic enzymes (Slominski, 1991a, Slominski et al., 1995, Slominski et al., 1996d, Slominski et al., 1992b, Slominski et al., 1993b, Slominski et al., 1993c). Over the last fifteen years our and other laboratories provided definitive evidence that skin expresses CRF and the POMC-derived β-endorphin, ACTH and α-MSH, the corresponding CRF1, melanocortin (MC) and opiate receptors, along with the key enzymes of corticosteroid synthesis, which results in the cutaneous production of corticosterone and cortisol (Arck et al., 2006, Rogoff et al., 2001, Slominski et al., 2004d, Slominski and Wortsman, 2000, Slominski et al., 2000c, Slominski et al., 2007a, Slominski et al., 2006b, Tobin, 2006, Tobin and Kauser, 2005b). Furthermore, we presented data indicating that CRF can stimulate cortisol production in skin cells via POMC cleavage products (Fig. 16) (Ito et al., 2005, Slominski et al., 2007a, Slominski et al., 2005e, Slominski et al., 2006b). These studies provided accumulating evidence that the cutaneous stress response system follows the functional hierarchy of the central HPA with its direct local phenotypic consequences and systemic implications (Slominski, 2009b, Slominski et al., 2008b, Slominski et al., 2007a) (Fig. 17).

Importantly, CRF, POMC and corresponding receptors were co-expressed in cultured keratinocytes, melanocytes or dermal fibroblasts (Slominski et al., 2000c, Slominski et al., 2006b) as well as their co-expression was demonstrated in vivo in the skin by in situ hybridization or immunocytochemistry (Funasaka et al., 1999, Ito et al., 2005, Kauser et al., 2006, Kono et al., 2001, Rogoff et al., 2001, Slominski et al., 2000c, Slominski et al., 2006b). Finally, the expression of the executive arm of the HPA, i.e. production of cortisol and corticosterone has been clearly demonstrated in cultured epidermal keratinocytes and melanocytes as well as in dermal fibroblasts (Hannen et al., 2011, Slominski et al., 2005d, Slominski et al., 2005e, Slominski et al., 2006b, Vukelic et al., 2011). Moreover, production of cortisol and corticosterone was also shown in human hair follicles maintained in vitro (Ito et al., 2005, Sharpley et al., 2009), and in rodent skin. In fact, skin contains an entire biochemical apparatus necessary to transform cholesterol to cortisol and corticosterone (Slominski et al., 2007a) including the capability to produce pregnenolone (Slominski et al., 2004d, Thiboutot et al., 2003) and its further sequential transformation to progesterone, deoxycorticosterone (DOC), 18-hydroxy-DOC, cortisol and corticosterone (Dumont et al., 1992, Ito et al., 2005, Rogoff et al., 2001, Slominski et al., 2000a, Slominski et al., 1999b, Slominski and Wortsman, 2000, Slominski et al., 2005d, Slominski et al., 2005e, Slominski et al., 2006b). The cutaneous expression of the above HPA axis elements is non-random, but is organized into functional, cell type-specific regulatory loops with a structural hierarchy similar to the central HPA (Slominski et al., 2007a) (Fig. 17). Specifically, exogenous CRF interacted with CRF1 on cultured human epidermal melanocytes and dermal fibroblasts stimulating cAMP production with subsequent increases of POMC gene expression and production of ACTH (Slominski et al., 2005e, Slominski et al., 2005d, Slominski et al., 2006b). Similarly, CRF stimulated POMC production in immortalized normal and malignant melanocytes expressing CRF1 receptor (Slominski et al., 2006b, Zbytek et al., 2006a), and

CRF stimulated POMC and αMSH production by epidermal and follicular melanocytes (Rousseau et al., 2007). Most importantly, normal human melanocytes responded to CRF, ACTH and factors raising intracellular cAMP with an increased production of cortisol and corticosterone, which was dependent on functional CRF1 receptor, since CRF1 receptor's antagonists abolished the effect, and on POMC expression, because silencing of the POMC gene abolished this effect (Fig. 16) (Slominski et al., 2005e). Thus, melanocytes, cells of neural crest origin, not only produce CRF, but also respond to it following an algorithm of the central HPA axis, adjusted to the local environment. While fibroblasts also responded to CRF and ACTH with enhanced production of corticosterone, cortisol levels were not regulated by axis, since cortisol was produced constitutively (Slominski et al., 2006b), thus indicating a partial departure from the classical algorithm of the HPA regulation.

The HPA components were also demonstrated in organ-cultured human scalp skin (Ito et al., 2005) where exogenous CRF increased POMC expression with sequential increases in ACTH and cortisol production. These were consistent with in situ co-localization of CRF, CRF1 and POMC in the skin and hair follicles (Kono et al., 2001, Rogoff et al., 2001, Slominski et al., 2000c). Exogenous cortisol inhibited CRF, MC2-R and ACTH expression by interacting with glucocorticoid receptors (Ito et al., 2005) which was in agreement with earlier studies which showed inhibition of the POMC and CRF expression by dexamethasone (a synthetic glucocorticoid) in mouse skin (Ermak and Slominski, 1997) and cultured human skin cells (Slominski et al., 1998b). Thus, mammalian skin expresses a fully-functional HPA axis equivalent which encompasses local CRF, ACTH and cortisol/corticosterone synthesis, and secretion with a negative feedback regulation of CRF and POMC expression mediated by glucocorticoid receptors' activation (Slominski et al., 2007a). The stimulatory role of ACTH on cortisol production by human epidermal cells has been confirmed recently (Cirillo and Prime, 2011a, Vukelic et al., 2011)

It is likely that the CRF-driven patterns of steroidogenic responses can be differential depending on cell subpopulation, their tissue localization and microenvironment (Fig. 10) (Slominski et al., 2007a). We have proposed a crucial role of paracrine communications in the skin where keratinocytes, melanocytes, fibroblasts, immune cells and nerve endings can serve as signal initiators (CRF, ACTH, cortisol or corticosterone) and recipients (binding to corresponding receptors) (Slominski, 2005a). The latter function would include an active and compartment-specific intercellular cross-talk and exchange of intermediates of the steroidogenic pathway.

7.3. Regulation of the cutaneous HPA axis

To serve a role of a coordinator and executor of local responses to stress, cutaneous homologue of the HPA should be activated by specific physical, chemical and biological skin stressors in organized fashion encompassing local production of CRF and POMC-derived peptides which interact with their respective receptors (Fig. 17). Indeed, an exposure of skin or skin cells to UVR stimulated in a time and dose dependent manner expression of CRF and POMC genes which was followed by the production and release of CRF, β-endorphin and ACTH peptides, expression of CRF1, PC1, MC2, MC1, CYP11A1 and CYP11B1, and production of cortisol (Chakraborty et al., 1999, Pisarchik and Slominski, 2001, Skobowiat et al., 2011, Slominski et al., 1996b, Zbytek et al., 2006b). The stimulatory effects were predominantly seen after exposure to UVB or UVC with only limited responses to UVA (Skobowiat et al., 2011).

In epidermal melanocytes the UVB-induced stimulation of the *CRH* promoter was suppressed by both the inhibitors of protein kinase A (PKA) and a plasmid overexpressing dominant mutant CREB (Zbytek et al., 2006b). Accordingly, UVB stimulated CREB phosphorylation, the binding of phosphorylated CREB to CRE sites in the CRF promoter

and the activity of the reporter gene construct driven by consensus CRE sites, while the mutation in the CRE site of the *CRF* promoter rendered the corresponding reporter gene construct less responsive to UVB (Zbytek et al., 2006b). In addition, pharmacological inactivation of CRF1 by selective inhibitors abrogated the UVB-stimulated induction of POMC (Zbytek et al., 2006b). These results indicate that UVR induces CRF 1 signaling by stimulating the PKA pathway with the subsequent stimulation of POMC production, which imitates HPA's organizational structure. Our most recent results also show that the ability to activate or modify the "cutaneous HPA" elements is dependent on highly energetic UV wavelengths (UVC and UVB) implying a dependence on their noxious activity (Skobowiat et al., 2011).

7.4. Functional activity of the cutaneous HPA

7.4.1. Local effects—All of the HPA elements (CRF and/or POMC signaling systems and steroidogenic activities), separately or in concert, can have profound phenotypic effects in the skin (Figs. 10, 17) (Slominski et al., 2000c, Slominski et al., 2007a, Slominski et al., 2006c) and may affect systemic body responses via neuroendocrine and hormonal signal transmission (Slominski, 2005a, Slominski et al., 2008b). In the skin these interactions can follow the classical pathway CRF→CRF1→POMC→ACTH→corticosterone/cortisol. However, the context-dependent departures from this central algorithm such as CRF→CRF1, CRF→CRF1→POMC, POMC→ACTH+MSH+β-END and POM→Ccorticosterone/cortisol may take place. The important local phenotypic outcomes of the entire axis or its departures are protective measures against environmental stressors (physical, biological, and chemical insults). This results from fine-tuning and selective regulation of skin pigmentation, barrier function, adaptive and innate immunity and adnexal structures' activity. The elements of the cutaneous HPA can also counteract skin pathology, such as inflammatory and autoimmune disorders as well as hyperproliferative and dysplastic processes, in order to protect and restore skin homeostasis. In this context non-endocrine activities of CRF and related urocortins make CRF signaling in the skin an important regulatory system. Similarly, a central role is assigned to the insult-regulated POMC expression and its context-dependent processing in the skin because the chemical nature of the final peptides defines the phenotypic effect (Slominski et al., 2004d, Slominski et al., 2000c, Slominski et al., 2007a). Finally, local steroidogenic activity would protect skin homeostasis, counteract pathologic processes but also, on the other hand, terminate protective responses to prevent their potential dyshomeostatic effects (Slominski, 2009, Slominski et al., 2007a, Slominski et al., 2008b).

7.4.2. Systemic effects—The possibility of the communication between local and systemic HPA axes as well as the differential activation of skin-derived axis' elements poses an interesting research question (Slominski, 2005a, Slominski et al., 2008c) due to the apparent evolutionary conservation of a similar organization at both central and peripheral levels (Slominski, 2007). Although all environmental factors noxious to the skin could participate in this communication (Slominski and Wortsman, 2000), the role of solar radiation in illustrating the above-mentioned communication and regulation of body homeostasis is the most instructive (Fig. 17) (Slominski et al., 2008b). Namely, UVR regulation of systemic homeostasis via HPA could include stimulation of CRF synthesis in the hypothalamus along neutrally-transmitted signals from the skin. An increased hypothalamic CRF release would automatically lead to the activation of the existing HPA with cortisol/corticosterone serving as final effector. The HPA axis could be entered at either the level of hypothalamus, pituitary or adrenal gland by skin-derived humoral messages including, respectively, cytokines (action on hypothalamus and/or pituitary), CRF/Urc 1 (action on the pituitary and, possibly, adrenal gland) or ACTH (action on the adrenal gland). This type of regulation would represent a fundamental paradigm shift in

neuroendocrinology and photobiology with profound implications for clinical medicine (see above and below).

These concepts are underscored by the observation that humans and horses exposed to sunlight led to increased serum levels of α-MSH and ACTH (Holtzmann, 1982, Holtzmann, 1983), while experimental whole body exposure to UVB increased β-LPH and β-endorphin serum levels (Belon, 1985, Levins et al., 1983). This model may provide mechanistic explanation for a well-known phenomenon of systemic immunosuppressive action of UVB (Kripke, 1994) or serve as an alternative explanation for the reported cases of the attenuation of multiple sclerosis in some patients after exposure to UVR, a phenomenon so far linked to the increased production of vitamin D (Becklund et al., 2010). Thus, our model of the UVR-mediated activation of central HPA axis may serve as a rational background for a phototherapy of systemic autoimmune disorders or other pathologies. Lastly, our model may provide mechanistic explanation of the recently described phenomenon of 'UVR addiction' (Kourosh et al., 2010, Nolan et al., 2009) caused by cutaneous β-endorphin production.

7.5. Common origin of the central and peripheral HPA

Evolutionary conservation of a similar HPA-like organization at central and peripheral levels has been documented (Arck et al., 2006, Slominski, 2005a, Slominski et al., 2004d, Slominski and Wortsman, 2000, Slominski et al., 2000c, Slominski et al., 2008c, Slominski et al., 2001, Slominski et al., 2007a, Slominski et al., 2006c). The common ectodermal origin of brain and epidermis raises the fundamental question of whether the peripheral CRF signaling system is an evolutionary duplicate of its central homologue or whether the brain itself has adopted the preexisting peripheral CRF response system during evolution of the central nervous and endocrine systems. Since it had been shown that cytokines and growth factors can modify CRF and POMC-related functions in pituitary and brain (Slominski et al., 2006c, Slominski and Wortsman, 2000) and that CRF can also act as a growth factor/cytokine (a function that develops at the periphery (Kauser et al., 2006, Slominski et al., 2006c, Slominski et al., 2006a, Zbytek and Slominski, 2007)), we proposed a new hypothesis on the integumental origin of the HPA axis (Slominski, 2007). We suggest that the primordial HPA (Fig. 18) had first developed in the integument to regulate its defensive activity against the hostile environment and pathogens. Key elements of this system include CRF-related peptide(s) that coordinate innate immune activity and skin barrier formation via CRF1 (an integrating receptor) and thus, both directly and indirectly, affect the expression of the proinflammatory cytokines such as IL-1 and TNFα. The feedback inhibitory loop begins with CRF1-activated POMC-derived production/secretion and culminates with the production/secretion of corticosterone/cortisol that 'shuts-off' HPA axis activity and inhibits skin barrier activity. The intermediate signaling molecules (POMC peptides) can both weaken the skin protective barrier by their immunosuppressive action and strengthen it by stimulating melanogenesis as well as direct anti-microbial effects. Thus, the protective barrier functions could be regulated and fine-tuned by the primordial HPA, because of the close association of all of its elements. During evolution, the main algorithm CRF>CRF1>POMC>ACTH>corticosterone/cortisol may have been adapted and perfected by the central neuroendocrine system to form the HPA axis which has separated anatomically and functionally from the immune system and the skin (Slominski, 2007, Slominski et al., 2008c, Slominski et al., 2007a). In this context the retained cutaneous HPA may serve as an evolutionary record of the primary system (Slominski, 2007) and, paradoxically, the systemic stress response can weaken the cutaneous antimicrobial defenses as a result of cortisol/corticosterone release from the adrenal glands (Aberg et al., 2007) (Fig. 18). It is also possible that both systems had derived from a common precursor and evolved in parallel maintaining neuro-immune-endocrine communication during this process

that has helped to preserve this fine organization of stress responses at the systemic and local levels.

7. 6. Conclusions

Many important elements of local and systemic responses to environmental stressors (biological, chemical and physical with predominant role of UVR) originate in the skin, and they involve multiple pathways encompassing activation of different components of the cutaneous and systemic HPA. Hence, signals generated by the integrated actions of CRF, POMC peptides, and cortisol/corticosterone may counteract the local effects of the environment. Furthermore, depending on the type of the stressor and its intensity, the skin can activate systemic HPA either via neural transmission by afferent nerve fibers to the brain or by skin-derived factors which may activate pituitary gland or directly act on the adrenal cortex (Fig. 17).

8. CUTANEOUS SECOSTEROIDAL SYSTEM

8.1. 7-Δ steroids

Few years ago it was shown that the P450scc system cleaves the side chain of 7-dehydrocholesterol (7DHC, pro-vitamin D3) to produce 7-dehydropregnenolone (7DHP) (Guryev et al. 2003; Slominski et al. 2004d). 7DHP is a substrate for a novel metabolic pathway for the synthesis of steroids with two double bonds in 5 and 7 positions, collectively called steroidal 5,7-dienes (Fig. 19), which, hypothetically, may be produced in the skin since cutaneous CYP11A1 (P450scc) expression was confirmed (Slominski et al., 2004d). The role of this new pathway was supported ex-vivo by demonstrating the efficient metabolic transformation of 7-dehydrocholesterol to 7DHP by adrenal glands and by mitochondria isolated from rat skin (Slominski et al., 2009c). HPLC separations, UV spectra and mass spectrometry identified 7DHP, 22-hydroxy-7DHC and 20,22-dihydroxy-7DHC as the major products with additional minor products defined as 17-hydroxy-7DHP and 7-dehydroprogesterone (Slominski et al., 2009c). These findings defined a novel steroidogenic pathway: 7DHC → 22(OH)7DHC → $20,22(OH)_2$7DHC → 7DHP, with potential further metabolism of 7DHP mediated by 3βHSD or CYP17 along the Δ_4 and Δ_5 steroidogenic pathways, with the production of 7-dehydroprogesterone and 17(OH)7DHP as intermediates (Slominski et al. 2009c). The existence of this synthetic pathway is documented by the accumulation of pregna-, and androsta-5,7-dienes and their hydroxylated derivatives in the Smith-Lemli-Opitz syndrome (SLOS), characterized by 7DHC Δ-reductase deficiency, an enzyme responsible for the conversion of 7DHC to cholesterol (Marcos et al., 2004, Shackleton et al., 2002, Shackleton et al., 1999, Tint et al., 1994). Most recently we have found that human placenta ex-utero can transform 7DHC to 7DHP and further to 7-dehydroprogesterone (Slominski et al., submitted for publication).

8.2. Secosteroidogenesis

The UVB-driven isomerization of 7DHC to vitamin D_3 [(3b,5*Z*,7*E*)-9,10-secocholesta-5,7,10(19)-trien-1a,3b,25-triol] is one of the most fundamental chemical reactions in vertebrates (Holick, 2003, Holick and Clark, 1978, Holick et al., 1995). This conversion is initiated by photolysis of the unsaturated B ring on absorption of UVB solar energy of 290–320 nm wavelength producing a pre-D_3 intermediate, followed by its slow isomerization to three main products: vitamin D_3, $tachysterol_3$ and $lumisterol_3$. The rate of isomerisation depends on the dose of absorbed UVB energy, wavelength, temperature, and the presence of biological membranes (Fig. 19) (Buchli et al., 2001, Holick et al., 1995, Tian and Holick, 1999). In response to high doses of UVB another pathway of vitamin D_3 degradation/isomerization yields 5,6-transvitamin D_3, as well as suprasterols I and II was also demonstrated in the skin (Buchli et al., 2001). In biological systems pro-vitamin D3

(7DHC) can also be transformed to 5,7,9(11)-trienes in a chemical process that involves an interplay between singlet oxygen and photosensitizers (Albro et al., 1994, Chignell et al., 2006, De Fabiani et al., 1996, Feng et al., 2006, Valencia and Kochevar, 2006).

The 5,7-dienal steroids described above as well as P450scc-derived hydroxyl derivatives of 7DHC undergo UVB-induced transformation to androsta-calciferols (aD) and pregna-calciferols (pD), and novel hydroxyderivatives of vitamin D_3 (Kim and Lee, 2010, Li et al., 2010, Slominski et al., 2009a, Slominski et al., 2004d, Slominski et al., 2009c, van Beek et al., 2008, Zmijewski et al., 2010, Zmijewski et al., 2011) (Fig. 20). Furthermore, P450scc also metabolizes vitamin D_3 to 20(OH)D_3, 20,23$(OH)_2D_3$, 22(OH)D_3, 20,22$(OH)_2D_3$, 17,20,23$(OH)_3D_3$ and several other D_3-hydroxyproducts. Novel P450scc-derived secosteroids show anti-proliferatory, antifibrotic and pro-differentiation activities in a cell type-restricted fashion that depends on the length of the side chain (Janjetovic et al., 2010, Janjetovic et al., 2009, Li et al., 2010, Nguyen et al., 2009, Slominski et al., 2009a, Slominski et al., 2009c, Slominski et al., 2010, Slominski et al., 2011b, Slominski et al., 2011d, Zbytek et al., 2008, Zmijewski et al., 2010, Zmijewski et al., 2009a). These compounds are anti-tumorigenic, can stimulate keratinocyte differentiation and inhibit NFκβ, acting by binding to vitamin D receptor (VDR) as its partial receptor agonists. They are as potent as 1,25$(OH)_2D_3$, however, unlike 1,25$(OH)_2D_3$, only weakly stimulate CYP24 expression (Janjetovic et al., 2010, Janjetovic et al., 2009, Slominski et al., 2009a, Zbytek et al., 2008). Importantly, 20(OH)D3 and 20,23$(OH)_2D_3$ did not affect calcium homeostasis at concentrations as high as 3–4 μg/kg (Slominski et al., 2010, Slominski et al., 2011b). Thus, we discovered novel metabolic pathways initiated by the enzymatic action of cytochrome P450scc (CYP11A1) that produces biologically active novel secosteroids or their precursors of which systemic and local significance, including their occurrence in the skin, remains to be defined.

8.3. Vitamin D activity in the skin: an overview

The role of skin in the physiology and pathology of vitamin D_3 and its derivatives was a subject of extensive reviews, therefore, below we present only short overview and refer the reader to more extensive descriptions (Bikle, 2011d; Bikle, 2011c; Bikle, 2011b; Bikle, 2011a; Denzer et al., 2011; Field and Newton-Bishop, 2011; Holick, 2008; Holick, 2003; Lehmann et al., 2004; Pinczewski and Slominski; Reichrath, 2007).

The epidermal keratinocytes are not only the site of the photochemical transformation of 7-dehydrocholesterol to vitamin D_3 but also possess the entire enzymatic machinery capable activating and inactivating vitamin D_3 and its derivatives. Vitamin D_3 is activated by sequential hydroxylation in position 25 by CYP27A1 and in position 1α by CYP27B1 to form calcitriol, i.e. 1,25$(OH)_2D_3$ [(1a,3b,5Z,7E)-9,10-secocholesta-5,7,10(19)-trien-1,3,25-triol)]. 1,25$(OH)_2D_3$ is inactivated by the action of CYP24 yielding 1,24,25$(OH)_3D_3$. The phenotypic effects of vitamin D_3 and some of its derivates are mediated by its interaction with vitamin D receptor (VDR) which is expressed in all skin cells including keratinocytes, melanocytes, fibroblasts and other resident cells of the skin. VDR belongs to the family of nuclear receptors and has ligand-activated pleiotropic activities including inhibition of cell proliferation, stimulation of cell differentiation and modulation of immune functions of skin resident and immigrant cells, to name the most important. Vitamin D is also involved in the regulation of skin barrier function, modulation of skin stress responses, regulation of hair follicle cycling, and suppression of tumorigenesis. To exert those pleiotropic effects VDR, after dimerization with RXR (retinoic acid receptor X) and translocation to the cell nucleus, interacts with the D receptor-interacting protein (DRIP), the steroid receptor coactivator (SRC) family proteins (with SRC2 and 3 expressed in keratinocytes), β-catenin and the inhibitor hairless protein (Hr) (Bikle, 2001a, b).

The gradient of calcium level in the epidermis, defined by its low content in the basal layer and the highest level in the corneal layer, determines the expression of several genes required for differentiation of the epidermis and proper epidermal barrier formation. The calcium-stimulated keratinocyte differentiation requires the activity of several proteins including calcium receptor (CaR), phospholipase PLC-γ1 and SRC kinases (Bikle, 2011a). Calcitriol, the active form of vitamin D_3, was shown to stimulate the expression of CaR, which subsequently sensitizes keratinocytes to calcium. Moreover, calcitriol is involved in the regulation of synthesis, processing and trafficking of glycosylceramides, which are important for the regulation of epidermal permeability barrier. In human keratinocytes calcitriol induces the expression of loricrin, filagrin, phospholipase PCL-γ1 and, synergistically with Ca^{+2}, increases the expression of involucrin and transglutaminase K (enzyme required for the cornification of keratinocytes). Anti-proliferative effects of calcitriol are also mediated by inhibiting c-myc, cyclin D1, p21 and p27 (Bikle, 2011a).

The pleiotropic effects of vitamin D_3 on skin physiology cannot be solely explained by the differential expression of VDR, which is the highest in the basal layer of the epidermis. As previously mentioned, the activity of VDR is modulated by its interactions with DRIP co-activator complex and SRC proteins. Moreover, it was also shown that in undifferentiated keratinocytes VDR preferentially binds to DRIP co-activator complex in contrast to the more differentiated epidermal cell layers, where VDR interacts with SRC proteins (Bikle, 2011a).

Vitamin D is also involved in the regulation of skin immune responses by stimulating the expression of IκBα, a NFκB inhibitor, which leads to the retention of NFκB in the cytoplasm and its subsequent degradation (Janjetovic et al., 2010; Janjetovic et al., 2009; Lu et al., 2004; Reichrath, 2007). Thus, vitamin D and its derivatives inactivate the major transcription factor responsible for the transcription and release of many inflammatory mediators. On the other hand, vitamin D can stimulate innate immune responses, including production of antimicrobial peptides (Gombart et al., 2005; Reichrath, 2007).

Basal and squamous cell carcinomas are the most frequent types of human cancer. Because vitamin D and its derivatives inhibit proliferation and stimulate differentiation of keratinocytes, its possible use in the treatment of skin cancer and hyperproliferative diseases of the skin, including psoriasis, has been suggested (reviewed by Bikle, 2011b; Bikle, 2011c; Holick, 2008; Lehmann et al., 2004). It is likely that hedgehog or β-catenin pathways can serve as targets of the anti-carcinogenic activity of vitamin D in the skin (Bikle, 2011c; Tang et al., 2011; Teichert et al., 2011). Furthermore, calcitriol and other derivatives of vitamin D show anti-melanoma activities, and defective expression of VDR correlates with poor prognosis of melanoma (reviewed by Berwick et al., 2005; Brozyna et al., 2011; Field and Newton-Bishop, 2011; Janjetovic et al., 2011; Pinczewski and Slominski 2010; Slominski et al., 2011).

8.4. Conclusions

We discovered a novel pathway initiated by the enzymatic action of CYP11A1 on 7DHC (provitamin D3), vitamin D3 and plant-derived ergosterol (provitamin D2) (Slominski et al., 2004d, Slominski et al., 2005f, Slominski et al., 2005g, Slominski et al., 2006d). The CYP11A1 metabolites of 7DHC, and hydroxyproducts of 7DHP generated by enzymes of classical steroidogenic pathway to produce 5,7-dienal steroids, can be converted by ultraviolet B radiation (UVB) to novel vitamin D hydroxyderivatives, androsta-calciferols and pregnacalciferols, which are biologically active in keratinocytes and melanoma cells (Janjetovic et al., 2010, Slominski et al., 2010, Slominski et al., 2011b, Zbytek et al., 2008, Zmijewski et al., 2010, Zmijewski et al., 2011). In addition, lumisterol- and tachysterol-like compounds are produced in the skin by the action of UVB. The biological activity of the

vitamin D-derived compounds is defined by their chemical structure and cell lineage. Since P450scc is expressed in the skin, we propose that novel secosteroidal pathways may affect skin biology with potent therapeutical implications. Moreover, body's global homeostasis can potentially be affected by skin-derived secosteroids as well as by CYP11A1-mediated hydroxylation of hydroxyvitamin D in organs or tissues which exhibit high activity of this enzyme.

The associations of vitamin D levels with various pathological states, including osteoporosis, rickets, coronary heart disease and carcinogenesis, have recently become the subject of intensive clinical investigations. It is hoped that the results of these studies will provide sufficient data to define the requirements for vitamin D dietary supplementation. Also, the newly-described low calcemic vitamin D derivatives, such as 20-OH D_3 may serve in the future for anticancer therapy.

9. EQUIVALENT OF HYPOTHALAMIC-PITUITARY-THYROID (HPT) AXIS

9.1. Overview

The hypothalamic-pituitary-thyroid (HPT) axis represents the central regulatory mechanism of cellular metabolism including protein, carbohydrate and lipid catabolism. The HPT axis is also involved in cell differentiation and proliferation as well as morphogenesis. Tight control of thyroid hormone activity is orchestrated by hypothalamic synthesis of the thyroid-releasing hormone (TRH), which activates its receptors (TRH-R1) in the anterior pituitary, followed by thyroid-stimulating hormone (TSH) secretion. TSH stimulates the production of 3,5,3′-triiodothyronine (T3) and thyroxine (T4) by thyreocytes. Elevated serum levels of thyroid hormones inhibit TRH and TSH synthesis by hypothalamus and pituitary, respectively (Fig. 21). Although T4 is the major thyroid hormone found in circulation, T3 is a fully active hormone since deiodinases (type 2 and 3) are expressed in a variety of tissues, including skin, facilitate the conversion of T4 to T3 (Fig. 21). Skin is a non-classical target for TSH, TRH and thyroid hormones.

9.2. HPT in the skin

The expression of the molecular elements of the HPT axis (genes for TSH-R1, TSH, TRH, TRH-R1, deiodinases 2 and 3, thyroglobulin, and sodium iodide transporter) in human skin and functional TSH receptors in keratinocytes and malignant melanocytes were first shown by Slominski et al. (Slominski et al., 2002e). Follow-up studies demonstrated TRH and TSH receptors' expression in various skin cell types including keratinocytes, melanocytes, fibroblasts, and in hair follicles (Bodo et al., 2010, Cianfarani et al., 2010, Gaspar et al., 2010, Pattwell et al., 2010, van Beek et al., 2008), which gave ground to the concept of a cutaneous HPT axis that would show similarities to and differences with the central HPT axis (Slominski et al., 2002e). The presence of TSH and TRH receptors explains the phenotypic changes in epidermal and dermal cells treated with TRH and TSH (Bodo et al., 2010, Cianfarani et al., 2010, Gaspar et al., 2010, Pattwell et al., 2010, Slominski et al., 2002e, van Beek et al., 2008). The interaction of T3 with its receptors (TRα and TRβ) affects epidermal differentiation and enhances its responsiveness to growth factors (Billoni et al., 2000, Slominski and Wortsman, 2000). These effects of T3 are particularly important for the function of sebaceous, eccrine, and apocrine glands, growth of hair follicles and synthesis of proteo- and glycosaminoglycans by dermal fibroblasts. For instance, both types of T3 receptors can regulate keratinocytes' proliferation, differentiation and immune activity (Contreras-Jurado et al., 2011). Results of the latter study suggest that thyroid hormones acting via their receptors can inhibit skin inflammation, most likely by inactivating specific transcription factors: AP-1, NF-κB and STAT3 (Contreras-Jurado et al., 2011). T4 stimulates the proliferation of hair follicle keratinocytes and T3 inhibits their apoptosis (van

Beek et al., 2008). Moreover, thyroid hormone receptors might suppress invasiveness and metastatic ability of skin tumors as shown in mouse knockout models (Martinez-Iglesias et al., 2009). Thyroid hormones may also affect hair follicle stem cells, since T3 and T4 were found to induce differentiation and apoptosis, and inhibit clonal growth of hair follicle epithelial stem cells (Tiede et al., 2010). The activity of deiodinases enables cutaneous conversion of T4 into T3, what plays a role in the regulation of the proliferation of keratinocytes and dermal fibroblasts in vitro and in vivo (Huang et al., 2011, Safer et al., 2009).

The effects of thyroid hormones in the skin are well pronounced in case of thyroid gland pathology including autoimmune thyroid disease (Cianfarani et al., 2010, Slominski and Wortsman, 2000). Dermal manifestations of hyperthyroidism include erythema, palmoplantar hyperhidrosis, acropathy, and infiltrative dermopathy. Moreover, Graves' disease also may be associated with generalized itching, chronic urticaria, presence of alopecia areata and vitiligo (Doshi et al., 2008, Ingordo et al., 2011, Kasumagic-Halilovic et al., 2011). Skin manifestations of thyroid disorders are in part correlated with elevated serum levels of thyroglobulin (Tg), thyroperoxidase (TPO) and thyroid-stimulating hormone receptor (TSH-R) antibodies (Cianfarani et al., 2010, Slominski and Wortsman, 2000). Conversely, in hypothyroidism the skin is cool, dry with pasty appearance; hair are commonly dry, coarse and brittle with up to a 50% probability of diffuse or partial alopecia development (reviewed by Slominski and Wortsman, 2000). Several studies also underlined the significance of TSH and TRH in the human skin and their influence on hair physiology (Bodo et al., 2010, Cianfarani et al., 2010, Gaspar et al., 2010). The physiological activity of TRH was demonstrated in human hair follicles' organ cultures expressing active TRH-R1 receptor. TRH stimulated hair shaft formation, prevented apoptosis, increased proliferation of hair matrix keratinocytes and prolonged the anagen phase of hair growth cycle (Gaspar et al., 2010, van Beek et al., 2008). TRH can also stimulate hair follicle pigmentation (Gaspar et al., 2011), probably by direct activation of melanocortin type 1 receptor (MC-1R), confirming our previous hypothesis (Slominski et al., 2005b, Slominski et al., 2002e). It was shown that TSH acting via TSH-R1 receptor increased cAMP production by human keratinocytes, human and hamster melanoma cells ((Slominski et al., 2002e) and enhanced the proliferation of epidermal keratinocytes and dermal fibroblasts (Bodo at al., 2010). Furthermore, TSH stimulated cyclic AMP production and altered the expression of several genes in human hair follicles and dermal papilla fibroblast cultures from normal female skin, however, did not affect hair growth and pigmentation (Bodo et al., 2009, van Beek et al., 2008). Expression of the TSH-R protein was detected in a wide panel of melanocytic lesions including melanoma. TSH activated the mitogen-activated protein kinase (MAPK) pathway and stimulated proliferation of melanoma cells, however, not melanocytes (Ellerhorst et al., 2010). Furthermore, TRH at low concentrations stimulated melanoma growth but not melanocytes' proliferation and its expression was increased in dysplastic nevi in contrast to benign nevi and was expressed in 63% of melanoma samples (Ellerhorst et al., 2006). Interestingly, other authors reported that suppression of MAP kinase and PI3K/Akt pathways, while leading to cell inhibition it induced thyroid genes' expression including TSH-R and sodium/iodide symporter, which led to increased iodine uptake by melanoma cells (Hou et al., 2009).

Recent studies demonstrated the expression of thyroid factor-1, thyroglobulin (Bodo et al., 2009) and thyroperoxidase in the human skin (Cianfarani et al., 2010). T3 and T4 were also shown to modulate the expression of cytokeratines 6 and 14 genes and down-regulate TGF-β2 expression in hair follicles (van Beek et al., 2008). Thyroid hormones also stimulated hair pigmentation (van Beek et al., 2008) and mitochondrial function by up-regulating the mRNA level of mitochondria-selective cytochrome-c-oxidase subunit 1 (MTCO1) and

significantly increasing complex I and IV (cytochrome-c-oxidase) activities in the epidermis (Poeggeler et al., 2010).

It is well established that thyroid dysfunction alters skin physiology, but expression of the equivalent of HPT axis in the skin raises also a possibility of a cross-talk between local and systemic counterparts as it was demonstrated in amphibians (Vaudry et al., 1999). These interactions might have long-range consequences, especially for the regulation of global homeostasis, evolution of skin stress response systems, and development of thyroid-related autoimmune diseases (reviewed by Slominski et al., 2008b). From the clinical point of view pathological exposure of TSH-R to immune cells in keratinocytes damaged by UVR or fibroblasts damaged during inflammation (Slominski et al., 2002e) can induce either production of anti-TSH-R antibodies leading to the uncontrolled stimulation of the thyroid gland or generation of anti-TSH-R clones of T lymphocytes - leading to immune destruction of the thyroid. These concepts, originally proposed by Slominski et al. (2002e), have been recently re-emphasized defining a role of skin in thyroid autoimmune diseases (Cianfarani et al., 2010).

9.3. Conclusions

Different elements of the HPT axis are expressed in the skin and this expression is skin cell-type dependent. The expression of individual or networked HPT elements can regulate skin phenotype in a differentiated and context-dependent manner (Fig. 21). Possibly, communication between the cutaneous HPT axis and other local neuroendocrine networks as well as with central coordinating centers takes place and affects global homeostasis (Figs. 1, 21).

10. CUTANEOUS OPIOID SYSTEM

10.1. An Overview

Endogenous opioid peptides derive from four different precursor proteins. Proopiomelanocortin (POMC) yields ACTH and endorphins, mainly β-endorphin (β-END). Proenkephalin (PENK) generates enkephalins (ENK) - predominantly Met-enkephalin (MENK) and Leu-enkephalin (LENK). The proteolysis of prodynorphin (PDYN) results in the formation of dynorphin A (DYN A) and B (DYN B) (Przewlocki, 2004, Przewlocki and Przewlocka, 2005). Another POMC derivatives are endomorphins which are the cleavage products of a larger precursor molecule that yet has not been identified (Fichna et al., 2007).

Three classes of the Gi/Go/Gq coupled opioid metabotropic receptor (OR) family have been identified: mu (μ, MOR), delta (δ, DOR), and kappa (κ, KOR). In addition, an orphan opioid-like nociceptin receptor (NOP), which has a 70% sequence homology with other opioid receptors, was also characterized (Jordan and Devi, 1998, Jordan et al., 2000, Przewlocki and Przewlocka, 2005, Salemi et al., 2005). Activation of ORs inhibits cAMP signaling as well as alters voltage-gated Ca^{2+} channel function and activates K^+ inwardly rectifying channels. The endomorphins bind to MOR with the highest affinity, ENK preferentially binds to the DOR and DYN favorably binds with KOR (Przewlocki, 2004). The ligand-receptor affinity presents in the following order: β-END μ, δ >κ; LENK/MENK δ, μ; DYNA κ>μ>δ (Jordan et al., 2000, Tominaga et al., 2007).

10.2. Opioid peptides in the skin

10.2.1. β-endorphin—It was shown that human and animal skin and/or cultured skin cells such as keratinocytes and melanocytes (normal and pathological) have the capability to transcribe and translate the precursor opioid protein genes (Nissen and Kragballe, 1997, Polakiewicz et al., 1992, Salemi et al., 2005, Sikand et al., 2011, Skobowiat et al., 2011,

Slominski et al., 1992b, Slominski et al., 1993b, Slominski et al., 2000c, Slominski et al., 2011c, Zagon et al., 1996). The POMC gene and protein, and POMC-derived peptides (ACTH, α-MSH and β-END) were detected in epidermis, dermis, adnexa and, additionaly, can be released from the cutaneous nerve endings (Hasse et al., 2007, Mazurkiewicz et al., 2000, Slominski et al., 1998a, Slominski et al., 1992b, Slominski et al., 2000c, Slominski et al., 1993c, Tobin and Kauser, 2005a, Wintzen and Gilchrest, 1996). The cutaneous expression of POMC was first found in rodent (hamster and mouse) melanomas (Slominski, 1991b) and in mouse (Slominski et al., 1992a) and human (Slominski et al., 1993c) skin, where the β-END antigen was detected as well.

β-endorphin stimulates keratinocyte migration in vitro (Grando et al., 1995, Tominaga et al., 2007), induces epidermal and follicular melanogenesis (Kauser et al., 2004) and also controls hair growth, wound healing and cellular differentiation (Schmelz and Paus, 2007). Furthermore, it increases modulates the number of dendritic processes of hair follicle melanocytes (Kauser et al., 2004). Some authors reported that plasma β-END levels increase after UV exposure, which would explain the euphoric behavior observed in beachgoers (Fallahzadeh and Namazi, 2009). Other authors could not observe this correlation (Wintzen et al., 2001). Recently, UVR-induced increase of β-END level has been observed in ex-vivo maintained human skin (Skobowiat et al., 2011) (Fig. 22).

10.2.2. Proenkephalin—The expression of the *PENK* gene and the subsequent processing of proenkephalin to MENK/LENK (in a cell type–dependent manner), was demonstrated in the skin by RT-PCR, Western blotting, immunocytochemistry, time-of-flight/liquid chromatography and mass spectroscopy (Slominski et al., 2011c). PENK immunoreactivity was markedly restricted to differentiating keratinocytes of the stratum spinosum and granulosum, whereas proliferating basal keratinocytes did not exhibit this immunoreactivity (Slominski et al., 2011c, Zagon et al., 1996). Furthermore, physical (UVB) and biological (lipopolysaccharide) stressors demonstrated cell type–specific time- and dose-dependent stimulation of *PENK* gene expression (Slominski et al., 2011c). Also, fetal mesenchymal skin cells expressed and produced significant amount of PENK, indicating its association with cell proliferation (Polakiewicz et al., 1992). MENK released from rat Merkel cells acted in an autocrine/paracrine fashion by the inhibition of cell granules release via decrease of intracellular Ca^{2+} concentration (Tachibana and Nawa, 2005). ENK plays a role in the differentiation of epidermal keratinocytes and has direct antimicrobial activities which contribute to the skin protective barrier against noxious factors (Nissen and Kragballe, 1997, Slominski et al., 2011c).

10.2.3 Dynorphins—PDYN and DYN A are expressed in human skin cells as well as in cutaneous nerve fibers (Grando et al., 1995, Hassan et al., 1992, Salemi et al., 2005, Taneda et al., 2011, Tominaga et al., 2007). They are responsible for pilomotor activity (Gibbins, 1992) and nociception. Enhanced production of DYN A was found in atopic dermatitis (Tominaga et al., 2007). Endomorphin 1 and 2 immunoreactivity was found in nerve fibers of the rat skin, however, the physiological function of these peptides still has to be detyermined (Barr and Zadina, 1999, Borzsei et al., 2008).

10.3. Opioid receptors and their function in the skin

Previous studies showed that not only opioid peptides but also their receptors were expressed in the skin (Grando et al., 1995, Nissen and Kragballe, 1997, Salemi et al., 2005, Tachibana and Nawa, 2005). These findings define skin as an active environment for opioid action. Ectoderm-derived cells, e.g. keratinocytes and melanocytes, express ORs, however, at much lower level (by a factor of 200–20,000) than neurons. MOR showed a stronger expression than DOR in keratinocytes but an opposite expression pattern was found in

mesenchyme-derived fibroblasts (Bigliardi et al., 1998). Furthermore, KOR was detected in fibroblasts and mononuclear blood cells of normal human skin and DOR was expressed in fibroblasts isolated from human skin (Salemi et al., 2005). Enhanced expression of DOR and KOR in the skin justifies the exploration of novel δ and κ acting compounds as specific targets for future opioid therapy. OR-induced signaling can affect cell differentiation, migration as well as cytokeratin and cytokine expression in human epidermis. Thus, opioid receptors may not only be involved in the regulation of normal skin homeostasis but also in wound healing and scar formation (Bigliardi et al., 2009, Slominski, 2003a).

Opioids are best known for their antinociception, which can also be initiated by the activation of ORs outside the central nervous system (Salemi et al., 2005). Their inhibitory activities are related to the ligand activation of Gi,o,q proteins which down-regulates adenyl cyclase activity and, eventually, inhibits protein phosphorylation (Chizhmakov et al., 2005). In addition, modifications of ion-channels' activity have further expanded the spectrum of opioid-induced biological action. All ORs couple to various Ca^{2+} channels and are known to inhibit their activity. Stimulation of ORs also increases potassium conductance across the cellular membranes (Jordan and Devi, 1998, Jordan et al., 2000). Opiates increase the release of dopamine via presynaptic inhibition of GABA release, which leads to a reward response, an effect observed in tanning-addicts (Harrington et al., 2006, Nolan and Feldman, 2009, Przewlocki, 2004). Inhibitory action of opiates on noradrenergic activity is mediated by MOR, and its activation enhances CRF production and release (Armario, 2010). Opioids exert immunomodulatory effects in peripheral tissues including skin by stimulating lymphocyte proliferation, antibody production, T and NK cell activity and chemotaxis of macrophages and granulocytes (Fallahzadeh and Namazi, 2009, Jankowska and Schomburg, 1998, Jordan and Devi, 1998, Mousa et al., 2007).

Opioids produced by skin cells may probably act as para- and autocrine modulators which influence gene expression. Additionally, they may enter the systemic circulation being transported by dermal veins, and interact with specific receptors localized on cutaneous nerve fibers (Bigliardi et al., 2009, Borzsei et al., 2008, Slominski and Wortsman, 2000, Slominski et al., 2000c). The last property is required for their analgesic and anti-inflammatory activity. Transduced nervous signals from peripheral tissues could be conveyed to dorsal root ganglia (DRG) sensory neurons. Thus, via synaptic inhibition neuropeptides like substance P (SP) and calcitonin gene-related peptide (CGRP), responsible for pain and inflammation, would be down-regulated and not delivered to skin (Borzsei et al., 2008, Slominski and Wortsman, 2000, Tobin, 2006). Furthermore, signals could be transferred via the nucleus of the solitary tract (NTS) to thalamus, hypothalamus, especially to paraventricular and arcuate nuclei, and amygdala where they could exert their systemic actions (Slominski et al., 2008b) and enhance the activity of the reward system (Armario, 2010, Przewlocki, 2004, Przewlocki and Przewlocka, 2005, Slominski, 2005, Slominski and Wortsman, 2000) (Fig. 23).

10.4. Opioid system and pruritus

It has been known for decades that analgesia resulting from MOR activation induces itch, most probably by reducing the inhibition of pain fibers, whereas MOR antagonists, such as naltrexone, inhibit itch (Yosipovitch, 2010). It is widely accepted that KOR activation suppresses, while MOR signaling stimulates itch (Bigliardi et al., 2009, Roosterman et al., 2006). This has led to the opioidergic system being targeted by new antipruritic medications (Patel and Yosipovitch, 2010, Schmelz, 2010). A novel KOR agonist, nalfurafine/TRK-820, revealed antipruritic activity in morphine-, histamine-, and substance P-induced animal scratching models (Ko and Husbands, 2009). The number of nerve fibers entering the epidermis tended to increase in approximately 40% of psoriatic patients claiming itch sensation compared to healthy controls (Taneda et al., 2011). There were no differences in

epidermal number of MOR and β-END amount; however, levels of KOR and DYN A were significantly decreased between healthy controls and psoriatic patients (Taneda et al., 2011). Interestingly, opioids were shown to act upon capsaicin-sensitive nerve fibers and inhibit the release of inflammatory neuropeptides such as SP, neurokinin A and CGRP, i.e. neuropeptides that are indirectly involved in eliciting pruritus by releasing the pruritogen histamine (Roosterman et al., 2006, Stander et al., 2002).

It was shown that UV-induced keratinocyte-delivered nerve growth factor (NGF), upon retrograde transport from skin towards dorsal root ganglion, enhanced the expression of neuropeptides SP and CGRP and up-regulated the number of MORs localized on cutaneous sensory nerve fibers (Mousa et al., 2007, Roosterman et al., 2006). UV radiation can induce β-END production by keratinocytes (Skobowiat et al., 2011, Wintzen and Gilchrest, 1996), which may explain the addictive behavior seen in frequent tanners (Fallahzadeh and Namazi, 2009). Recent studies have provided evidence that, indeed, there are itch-specific receptors in the skin. Using *in vitro* binding assays, it was observed that the proteolytically-cleaved product of proenkephalin A, the bovine adrenal medulla peptide 8–22 (BAM8–22), potently activated the Mrgprs (Mas-related G-protein-coupled receptors) in an opioid-independent mechanism (Sikand et al., 2011).

10.5. Opioids and addiction

UV exposure during indoor tanning damages DNA, thereby leading to premature skin ageing and the development of skin cancer as well as malignant melanoma (Harrington et al., 2006). The majority of beachgoers reported behaviors consistent with those of an addictive disorder like continuation of tanning despite attempts to stop, persistent tanning in the presence of adverse reactions and the neglect of other responsibilities in order to maintain a tan (Keen et al., 2008). Psychological dependence is suggested by tanners' reports of relaxation and positive mood effects as a result of UV exposure. These observations may be explained by UV–induced production of cutaneous β-END (Skobowiat et al., 2011) resulting from local transcription, translation and further cleavage of POMC leading to the production of β-END (reviewed by Slominski, 2003, Slominski et al., 1993b, Slominski et al., 2000c).

Solar UV energy adsorbed by the epidermis also results in the transformation of a chromophore-like trans-urocanic acid to its cis-isomer, which reportedly could have an agonistic activity on serotonin receptor 2A (5HT2A) (Walterscheid et al., 2006). Thus, UV light can also alter cutaneous serotoninergic system with subsequent effects on the CNS affecting the mood (Harrington et al., 2011, Kourosh et al., 2010, Slominski et al., 2005c). Upon UV exposure, 5-HT could be transported from the skin via its blood vessels or activate ascending nerve fibers which affect brain activity (Nordlind et al., 2008, Slominski et al., 2005c). Specifically, brain striatal regions, including the nuclei accumbens, caudate and putamen, could be activated during UVR exposure (reviewed in Kourosh et al., 2010). Frequent tanning may involve CNS reward and/or reinforcement over the often-stated goal of 'getting a tan'. The ventral striatum (or nucleus accumbens) activation is typically associated with drug-induced reward observed in cocaine and nicotine smokers (Harrington et al., 2006). In fact, the term "psychodermatology" is being used to describe the mind–skin connection (Reich et al., 2010). From an evolutionary perspective, it is reasonable to suggest that sunlight may have central rewarding properties (Figs. 1, 23) given the importance for human health of UV-mediated vitamin D synthesis.

10.6. Conclusions

Opioids constitute a heterogeneous family of active peptides which play important roles in cutaneous nociception, immunomodulation, signal transduction and evoking or attenuating

of pruritus, depending on differential receptor activation. Their main inhibitory properties are related to the inhibition of cell membrane calcium channels that suppress the release of proinflammatory and pain transmitters like SP and CGRP. Both exogenously applied and endogenous opioids interact with a whole range of receptors and contribute to the neuroendocrinological functions of the skin, also at the systemic level (Figs. 1, 2, 23).

11. CUTANEOUS ENDOCANNABINOID SYSTEM

11.1. General overview

Endocannabinoids (ECS) constitute lipid mediators (amides, esters, and ethers of long chain polyunsaturated fatty acids) acting similarly to the exogenous Δ_9 tetrahydrocannabinol (Δ_9-THC; the main psychoactive ingredient of the plant *Cannabis sativa*), which are produced by humans and animals (Maccarrone et al., 2003, Rahn and Hohmann, 2009). The cutaneous ECS system is fully functional due to the expression of ECS with corresponding receptors and ECS degrading enzymes, which together participate in the proliferation, differentiation, growth, and apoptosis of skin cells as well as tumorigenesis and cytokine production in the skin (reviewed by Biro et al., 2009, Kupczyk et al., 2009, Toth et al., 2011). ECS are synthesized 'on demand' at the place of their action by receptor-stimulated cleavage of membrane lipid precursors and are not stored in synaptic vesicles that distinguish them from typical neurotransmitters. Re-uptake of ECS may be facilitated by a transporter that has yet not been cloned, however, the pharmacological inhibitors of ECS transport have nonetheless been developed (Guindon and Hohmann, 2009). The lipophilic nature of ECS allows them to activate enzymes in cytosol and membrane compartments, where they can interact with lipoprotein structures (Kupczyk et al., 2009).

The most extensively studied ECS are arachidonoylethanolamide (anandamide/AEA), 2-arachidonoylglycerol (2-AG) and N-palmitoylethanolamide (PEA), as well as their degradation enzymes like fatty acid amid hydrolase (FAAH) and the monoacylglycerol lipase (MGL).

11.2. Endocannabinoid Receptors

11.2.1. Characterization—Two receptor types for cannabinoids, CB1 and CB2, were identified, however, some researchers assume the existence of a third one, CB3, which has yet not been cloned (Kupczyk et al., 2009). The amino acid sequences of CB receptors are conserved through many species, including humans (Kupczyk et al., 2009). CB1 is predominantly expressed in central nervous system and also in other tissues, and CB2 was found mainly in non-neuronal cells and tissues, related to the immune system like lymphocytes, macrophages, spleen, and thymus. In the skin both receptor types are expressed on nerve endings, cutaneous mast cells, epidermal keratinocytes and adnexa (Biro et al., 2009, Maccarrone et al., 2003). Classical activation of CBs, which belong to the Gi/o family of G proteins, inhibits calcium channels as well as inward rectifying potassium conductance channel or involves MAPK activity (for CB2) that ultimately decreases production of cAMP, suppresses neuronal excitability and transmitter release. Furthermore, CB1 receptor activation can inhibit 5-HT3 ion channel receptor conductance, alter sodium channel activity, activate the Na^+/H^+ exchanger and modulate the production of NO (Guindon and Hohmann, 2009, Rahn and Hohmann, 2009). It was shown that CB1 and transient receptor potential vanilloid-1 (TRPV-1) are co-localized on sensory nerve endings in the skin (Akerman et al., 2004), thus, ECS, except for regular the activation of specific receptors, can also activate TRPV-1 in the skin (Karst et al., 2010, Maccarrone et al., 2003). This activation could lead to the alterations in vasodilatation, CGRP and SP release and nitric oxide (NO) synthesis (Fitzsimons et al., 2002, Toth et al., 2011).

11.2.2. Central effects of ECS—CB1 was shown to be localized presynaptically on GABA-ergic and glutamatergic interneurons (Kupczyk et al., 2009). The activation of CB1 results in decreased release of neurotransmitters such as GABA (γ-aminobutyric acid) or glutamate. This retrograde signaling mechanism suggests an important modulatory role for ECS in controlling neuronal excitability and maintaining homeostasis. ECS serves to facilitate adaptation to stress by restraining HPA axis response and maintaining homeostasis of the body (Finn, 2010).

11.2.3. Effects on proliferation and differentiation—CB1 agonists inhibited proliferation of cultured human epidermal keratinocytes, and AEA (*N*-arachidonoylethanolamide) markedly inhibited cell growth and induced dose- and CB1-dependent apoptosis in human HaCaT cells (Paradisi et al., 2008, Toth et al., 2011). AEA inhibited hair shaft elongation and the proliferation of hair matrix keratinocytes (Telek et al., 2007). Cannabinoids also induced intraepithelial apoptosis and premature hair follicle regression (characteristic signs of catagen transformation in hair follicles), processes that could be inhibited by a selective CB1 antagonist (Pucci et al., 2011; Toth et al., 2011). CB1 is expressed in a hair-cycle-dependent manner and acts as the negative regulator of human hair growth in an autocrine–paracrine way. Indeed, it was showed that CB1 receptor antagonists induced hair growth in mice (Srivastava et al., 2009).

Differentiating human keratinocytes have decreased levels of endogenous AEA, due to increased degradation of this lipid. In addition, it was shown that exogenous AEA inhibited keratinocyte differentiation in vitro, acting by a CB1-dependent mechanism that involved inactivation of protein kinase C, activating protein-1, and transglutaminase (Maccarrone et al., 2003). The high expression of CB1 in granular and spinous epidermal layers, suggest its involvement in the process of keratinocytes' differentiation (Stander et al., 2005).

11.2.4. Effects on tumorigenesis—Various human skin tumors (e.g. basal cell and squamous cell carcinomas) express both CB1 and CB2 receptors (Casanova et al., 2003, Zheng et al., 2008). Local administration of synthetic CB1 and CB2 agonists inhibited growth of skin malignant tumors by increasing intra-tumor apoptosis and impairing tumour vascularization (Casanova et al., 2003). ECS were also reported to inhibit in vivo growth of melanomas that expressed CB1 and CB2 by decreasing growth, cell proliferation, angiogenesis and metastasis formation, while increasing apoptosis (Blazquez et al., 2006). The local activation of cannabinoid CB1 and CB2 receptors, which are expressed in normal skin and skin tumors, induced the apoptotic death of tumorigenic epidermal cells, suppressed proliferation of melanoma cells and inhibited the growth and angiogenesis in the skin (Zheng et al., 2008). The UV irradiation alters the structure of keratinocyte's cell membrane as a result of energy absorption. UVB and UVA increased the affinity of CB1 and CB2 receptors for agonists and UVB also induced CB1 and CB2 phosphorylation and internalization in keratinocytes. membrane preparations (Zheng et al., 2008).

11.2.5. Effects on inflammation—The activation of CB2 receptors expressed mainly on immune cells decreaseD their metabolism during inflammation suggesting anti-inflammatory properties, reviewed by Pacher and Mechoulam (2011). Also in a mice model of contact allergy the cutaneous inflammation was suppressed by local Δ_9-THC administration or CB1 agonist (Karsak et al., 2007). Elevated 2-arachidonoylglycerol (2-AG) levels accompanied dermatitis in mice and the symptoms of inflammation were markedly attenuated by CB2 (but not CB1) agonists (Oka et al., 2006). Decreased dermal fibrosis and inflammation was observed upon treatment with the CB2 agonist, suggesting a potential therapeutic utility of selective CB2 agonists for the treatment of early inflammatory stages of systemic sclerosis (Akhmetshina *et al.*, 2009).

11.2.6. Effects on pain sensation—Enhanced activity of the nociceptive pathways is associated with increased levels of the ECS, particularly AEA, in dorsal root ganglion and spinal cord as well as in amygdala (Connell et al., 2006). Importantly, there is evidence for augmented peripheral ECS-mediated control of the mechanosensitivity of afferent nerve fibers (Sagar et al., 2010). Antinociceptive responses to foot shock stress occur downstream of receptor interactions in the amygdala (Connell et al., 2006). Elevated levels of ECS in models of chronic pain are likely to counteract the increased neuronal activity driven by afferent input and, therefore, may provide inhibitory modulation of the mechanisms driving central sensitization. Maintenance of these elevated levels of ECS by the manipulation of catabolic enzymes is effective for decreasing pain perception (Sagar et al., 2010). However, the antinociception mechanisms of ECS action remain unknown. Both AEA and 2-AG can be metabolized by cyclooxygenase-2, which may contribute to the analgesic properties of nonsteroidal anti-inflammatory drugs acting via the inhibition of cyclooxygenase (Rahn and Hohmann, 2009). Antinociceptive effects of CB1/2 agonists but also of FAAH inhibitors, which prolong the action of ECS, were reported (Karst et al., 2010, Rahn and Hohmann, 2009). Prolonged ECS action resulting from the inhibition of FAAH activity is likely to be more beneficial compared to the direct activation of CB1 receptors, however, the effects of FAAH deactivators are limited to sites where ECS are mobilized under physiological conditions in a stimulation-contingent fashion (Guindon and Hohmann, 2009). ECS and exogenous cannabinoids suppress nociceptive transmission, especially at the level of the posterior horn of the spinal cord (Finn, 2010, Karst et al., 2010). Low concentrations of anandamide reduced the capsaicin-induced CGRP release from rat skin, whereas higher concentrations directly stimulated CGRP release from an isolated rat trachea preparation; the latter effect was blocked by the competitive TRPV1 antagonist capsazepine (Engel et al., 2011)

11.2.7. Effects on itch—Pruritus as an unpleasant cutaneous sensation associated with the immediate desire to scratch may be interpreted as part of the body's defense mechanisms (Steinhoff et al., 2006). Stimulation of pruriceptors conveys the signal via histamine-positive mechano-insensitive C-fibers originating in DRG up to itch-selective units in lamina I of the spinal cord and finally to the posterior part of the ventromedial thalamic nucleus, which projects to the dorsal insular cortex. In contrast to pain, itch seems to be characterized by a lack of secondary somatosensory cortex activation in the parietal operculum and by left hemispheric dominance (Steinhoff et al., 2006). ECS stimulated the release of β-END from keratinocytes, thereby activating sensory neurons which led to the modulation of pain sensation (Ibrahim et al., 2005). Thus, it is evident that deregulation of skin function (e.g. by trauma, disrupted barrier function, inflammation, or UV radiation) can directly or indirectly stimulate sensory nerve endings (Roosterman et al., 2006, Slominski and Wortsman, 2000), thereby inducing pruritus (Yosipovitch, 2010). Different triggering factors are capable of stimulating the release of pruritogenic or antipruritogenic factors from keratinocytes. Therefore, it was suggested that CB2 receptor activation produced antinociception by stimulating β-END release from keratinocytes, which, in turn, elicited antinociception by acting at opioid receptors on primary afferent neurons (Ibrahim et al., 2005). Also in humans peripheral administration of cannabinoid receptor agonists attenuated histamine-induced itch (Dvorak et al., 2003). Subsequently, the CB2 inverse agonist, N-palmitoylethanolamine has been incorporated into creams with relief of pruritus reported in patients with atopic dermatitis, lichen simplex, and prurigo nodularis (Kircik, 2010). These promising preliminary results lead one to believe that new therapies that target cannabinoid receptors may lead to the development of effective antipruritic treatments in the future.

11.2.8. Conclusions—The recently described cutaneous endocannabinoid system expands skin's neuroendocrine properties. Endocannabinoidcs participate in the skin in a

wide spectrum of pathophysiological processes revealing anti-inflammatory, anti-tumorigenic, anti-nociceptive and anti-pruritic properties. ECS interact with two specific receptors which leads to the inhibition of synaptic transmission. Furthermore, ECS can interact with other receptors (opioid, serotonin, TRPV) by non-specific binding, modulating the release of other neurotransmitters and hormones. By these means ECS can participate in the regulation of the cutaneous and systemic homeostasis (Figs. 1, 2).

12. PERSPECTIVES

Described as the body's largest organ, the skin is strategically located at the interface with the external environment where it has evolved to detect, integrate and respond to a diverse range of stressors including UV radiation. Recent findings have established the skin as a peripheral neuroendocrine organ that is tightly networked to central stress axes (Fig. 2). This capability contributes to the maintenance of skin's and body's homeostasis. Specifically, epidermal and dermal cells produce and respond to classical stress neurotransmitters, neuropeptides and hormones, and this production is modified by ultraviolet radiation and biological, chemical and physical factors. Examples of potent epidermal products include biogenic amines (catecholamines, serotonin and N-acetyl-serotonin) (Figs. 3–5), acetylcholine, melatonin and its metabolites (Figs. 7, 8), proopiomelanocortin-derived ACTH, β-endorphin and MSH peptides, corticotropin-releasing factor and related urocortins (Figs. 10, 11, 17, 18), corticosteroids and their precursor molecules, thyroid-related hormones (Fig. 21), opioids and cannabinoids. The production of these molecules in the skin is hierarchical, following the algorithms of classical neuroendocrine axes (e.g. hypothalamic pituitary adrenal axis (HPA), hypothalamic-thyroid axis, serotoninergic/melatoninergic, catecholaminergic and cholinergic systems). The deregulation of these systems may be involved in the etiology of some skin diseases. These local neuroendocrine systems represent exquisite regulatory levels addressed at restricting the effect of noxious agents to preserve local and, consequently, global body's homeostasis and adapt to changing external environment. Furthermore, the skin-derived signals may also activate cutaneous sensory nerve endings to alert the brain on environment- or pathology-induced changes in the epidermal and dermal milieau, or alternatively, to activate other coordinating centers by spinal cord neurotransmission with, or without brain's involvement (Fig. 1). Finally, the local neuroendocrine system will imprint resident and circulating immune cells to act as cellular messengers sent to other organs to coordinate responses to the changing environment (Fig. 1).

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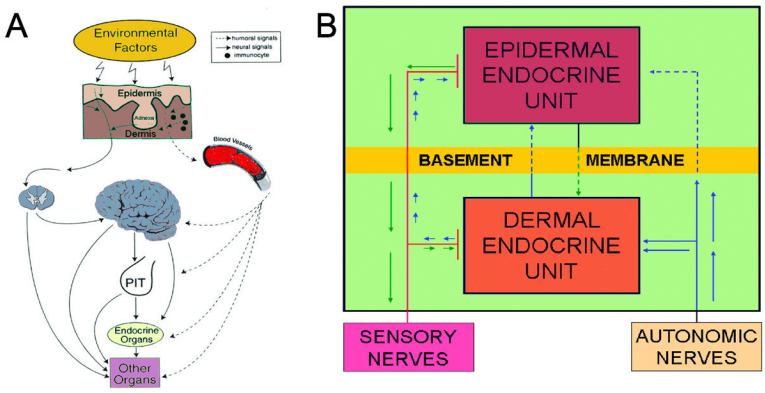

Figure 1.

Skin senses changes in the environment through cutaneous neuroendocrine system, which computes and translates the received information into chemical, physical and biological messengers that regulate global (A and B) and local (B) homeostasis. These signals travel through humoral, immune or neural pathways to reach the central nervous, endocrine and immune systems as well as other organs. Reproduced with permission from Endocrine Society (Slominski and Wortsman, 2000a).

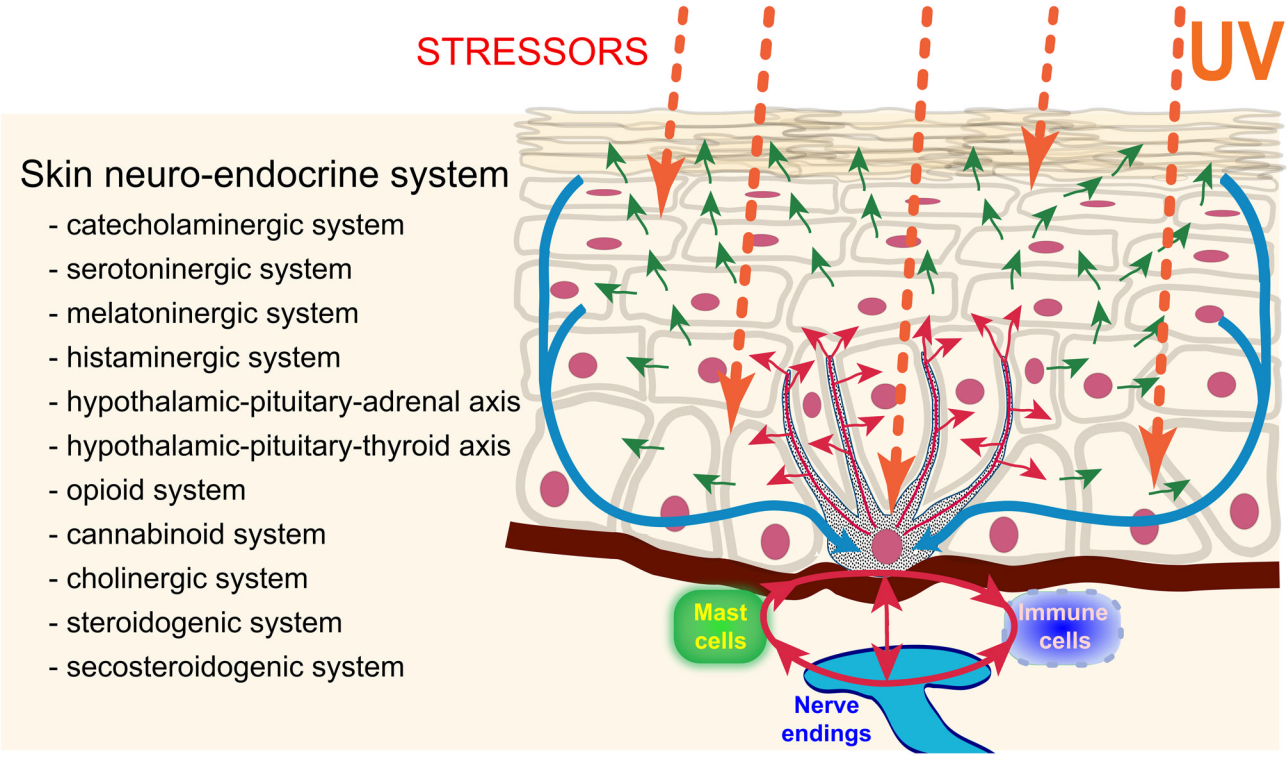

Figure 2.
Skin neuroendocrine system follows the algorithms of classical neuroendocrine or endocrine systems. It also forms a natural platform of signal exchange between internal organs and environment. For this purpose skin cells not only are subjected to neurohormonal regulation but also do produce neuropeptides, biogenic amines, melatonin, opioids, cannabinoids, acetylcholine, steroids, secosteroids as well as growth factors and cytokines. Skin neuroendocrine system also entrains immune cells to act as cellular messengers at distal sites.

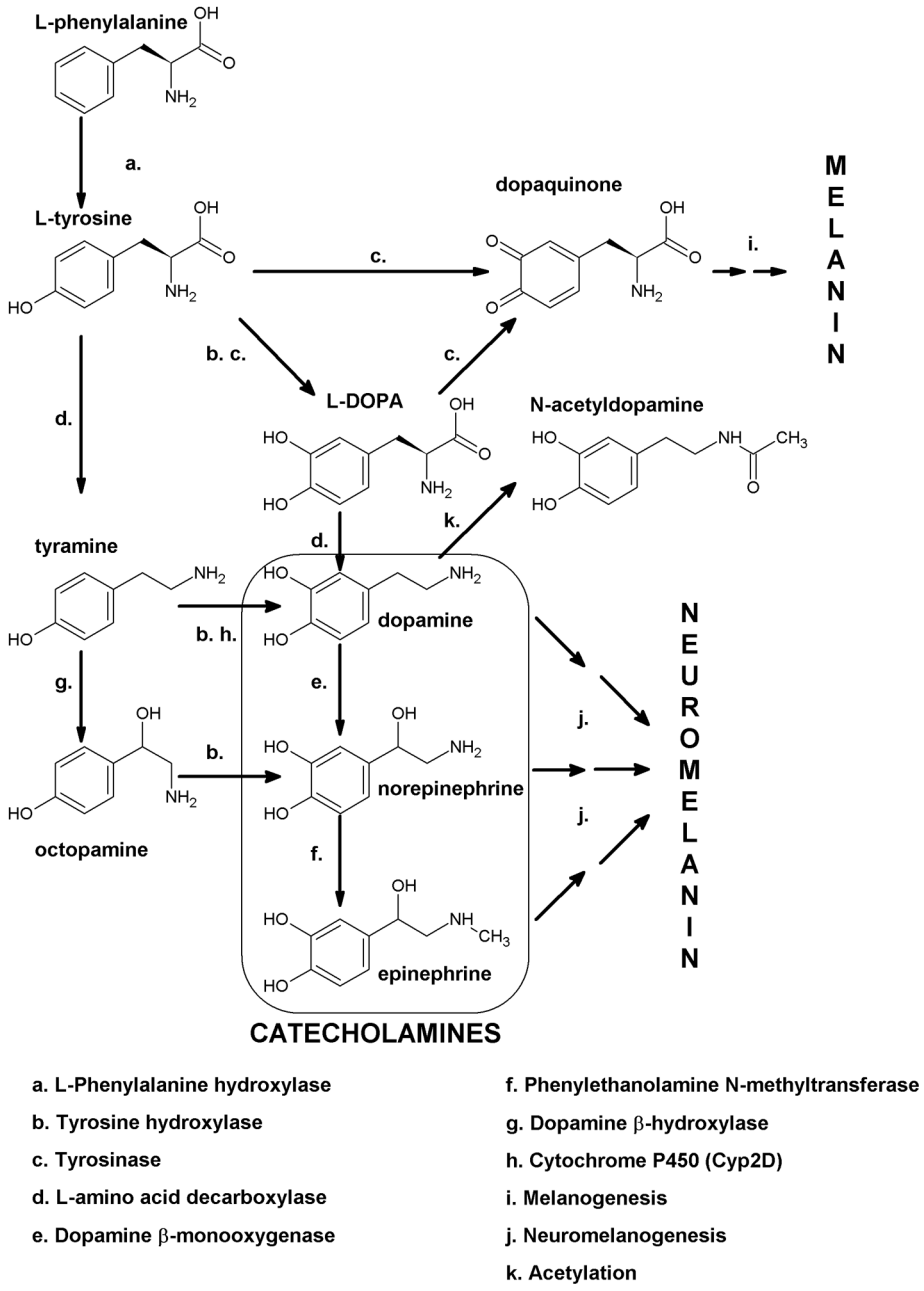

Figure 3. Catecholamine synthesis in the skin

The common pathway in the skin requires its consecutive hydroxylations of L-phenylalanine (mediated by phenylalanine hydroxylase (PH)) to L-tyrosine with following hydroxylation by tyrosine hydroxylase (TH) or tyrosinase to produce L-dihydroxyphenylalanine (L-DOPA). L-DOPA is either oxidized to DOPA quinone with following multistep transformation to melanin or serves as a substrate for synthesis of catecholamines. The skin expresses complete enzymatic machinery required for dopamine synthesis (L-amino acid decarboxylase - AAD) and its subsequent conversion into norepinephrine (dopamine β-hydroxylase) and methylation (phenylethanolamine N-methyltransferase) to form epinephrine. An alternative pathway of catecholamine synthesis involves decarboxylation of L-tyrosine to tyramine, which in turn is hydroxylated by TH (and Cyp2D) or dopamine β-

hydoxylase to octopamine or dopamine, respectively. Octopamine could be metabolized to norepinephrine by TH. This alternative pathway present in invertebrates remains to be tested in the skin. Catecholamines also undergo oxidation to corresponding quinoinones with further multistep transformation to neuromelanin that is similar to melanogenesis starting from L-DOPA.

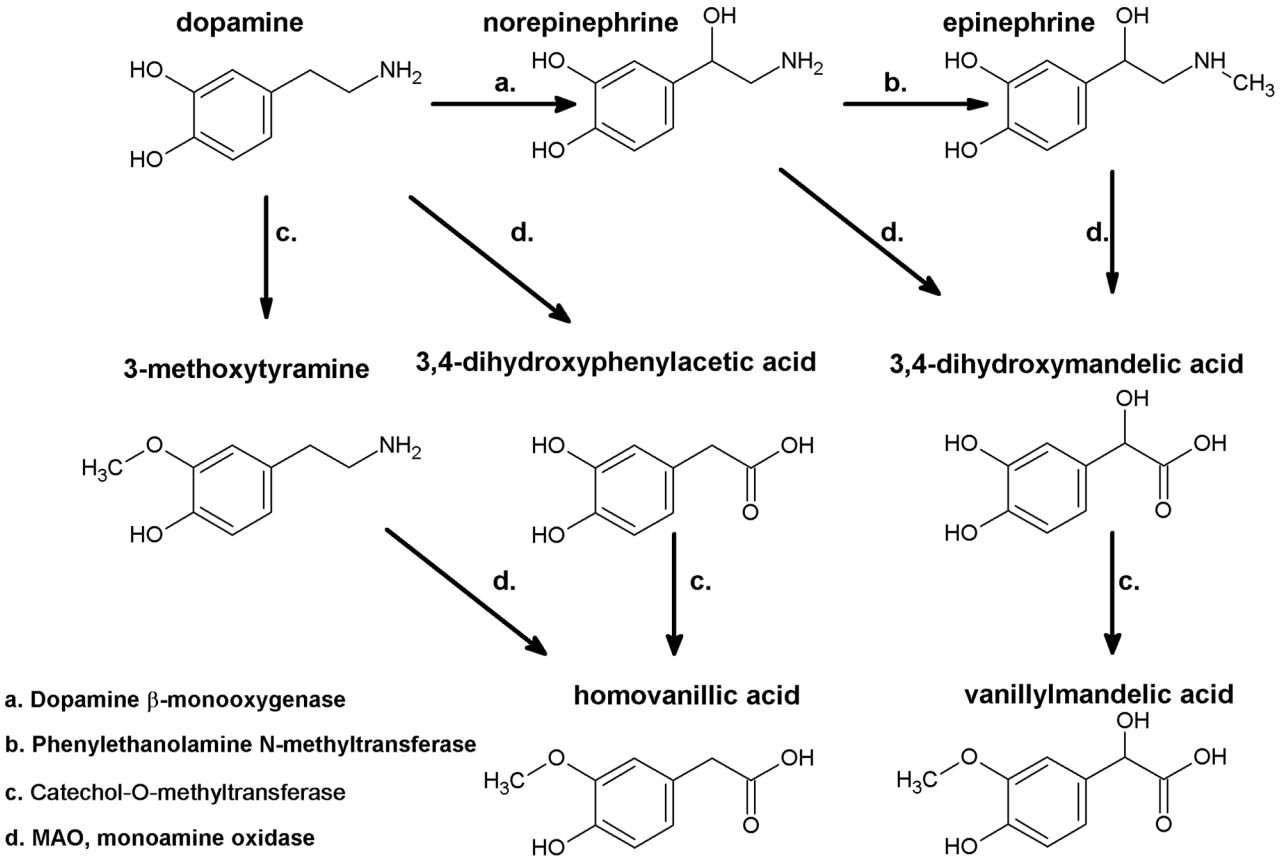

Figure 4. Catecholamine catabolism

Catecholamines are deactivated by L-monoamine oxidase (MAO) and Catechol-O-methyltransferase (COMT) leading to synthesis of homovanillic acid (from dopamine) or vanillylmandelic acid from norepinephrine or epinephrine. Alternatively, as shown for dopamine metabolism order of reaction may be change with COMT acting first followed by MAO.

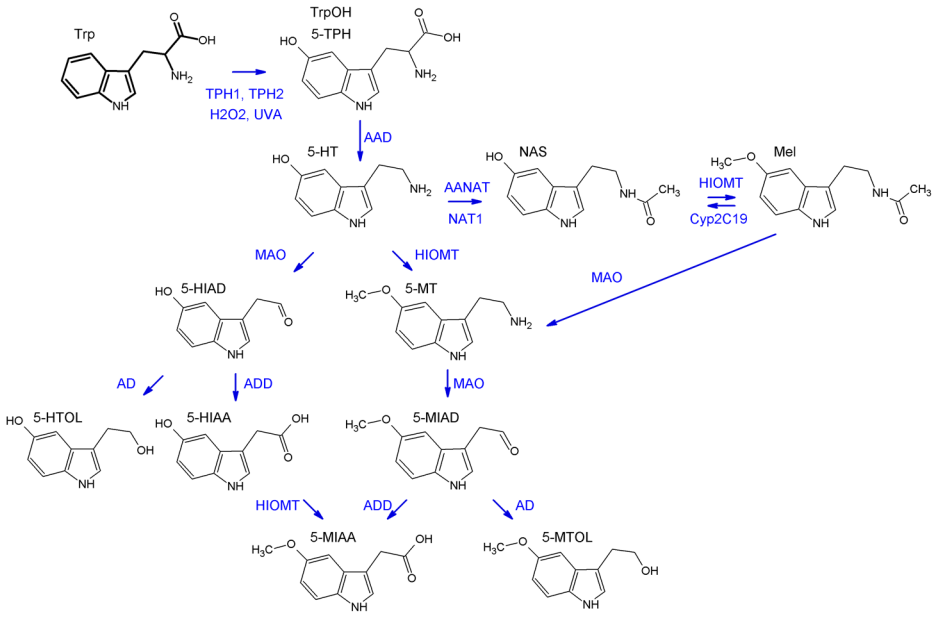

Figure 5. Biochemical pathway of serotonin synthesis and metabolism in the skin

The pathway starts with hydroxylation of tryptophan by tryptophan hydroxylase type 1 or 2 (TPH1 or TPH2) to form 5-hydroxytryptophan (5-TPH; TrpOH). TrpOH can also be produced by non-enzymatic action of UVA and H2O2. Serotonin (5-hydroxytryptamine, 5-HT) derives from 5-TPH by action of L-amino acid decarboxylase - AAD. Serotonin can be acetylated by aralkylamine N-acetyltransferase (AANAT) or N-acetyltransferase (NAT) to produce N-acetylserotonin (NAS) with further methylation by hydroxy-indole-O-methyl transferase (HIOMT) to melatonin. Deactivation of serotonin is catalyzed mainly by MAO with formation of 5-hydroxyindoleacetaldehyde (5-HIAD) which is followed by action of alcohol (AD) or aldehyde dehydrogenase (ADD) with formation of 5-hydroxytryptophanol (5-HTOL) or 5-hydroxyindole-3-acetic acid (5-HIAA), respectively. Alternatively, HIOMT activity may also lead to production of methylated derivatives of serotonin. First step catalyzed by HIOMT leads to formation of 5-methoxytryptamine 5-MT and subsequent action of MAO results in 5-metoxyindoleacetaldehyde (5-MIAD). Finally, AD or ADD facilitates synthesis of 5-methoxytryptophol (5-MTOL) or 5-methoxyindole-3-acetic acid (5-MIAA), respectively. HIOMT was found also to catalyze conversion of 5-HIAA to 5-MIAA. Melatonin by action of MAO can be metabolized to 5-methoxytryptamine (5-MT), thus entering the pathway leading to 5-MTOL or 5-MIAA formation.

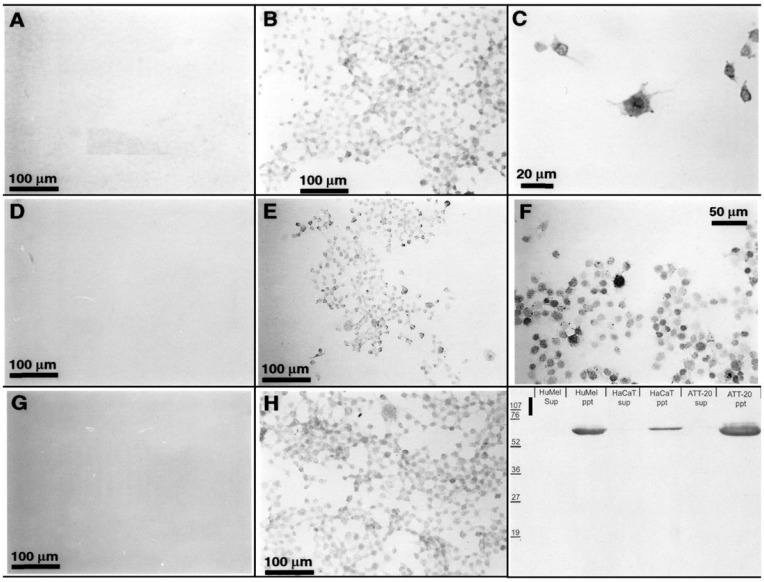

Figure 6. Expression of TPH, serotonin (5-HT) and serotonin transporter (5-HTT) in skin cells

Panels A-H show immunocytochemical detection of 5-HT (B, C), 5-HTT (E, F) and TPH (H) in fixed cells using corresponding antibody at dilution 1:5,000 (Antibody against 5-HT, Diasporin Corp., Stillwater, MN) or 1:1,000 (antibodies against TPH and 5-HTT, Chemicon, Temecula, CA). A, D, G: negative controls incubated with secondary antibody only. I. Western blot showing detection of 5-HTT in membranous (ppt) but not cytosolic (sup) fractions from human melanoma (HuMel), HaCaT keratinocytes (HaCaT) and ATt-20 pituitary (ATT-20) cells. For technical details of immunocytochemistry, or western blot assay see (Slominski et al., 2005d).

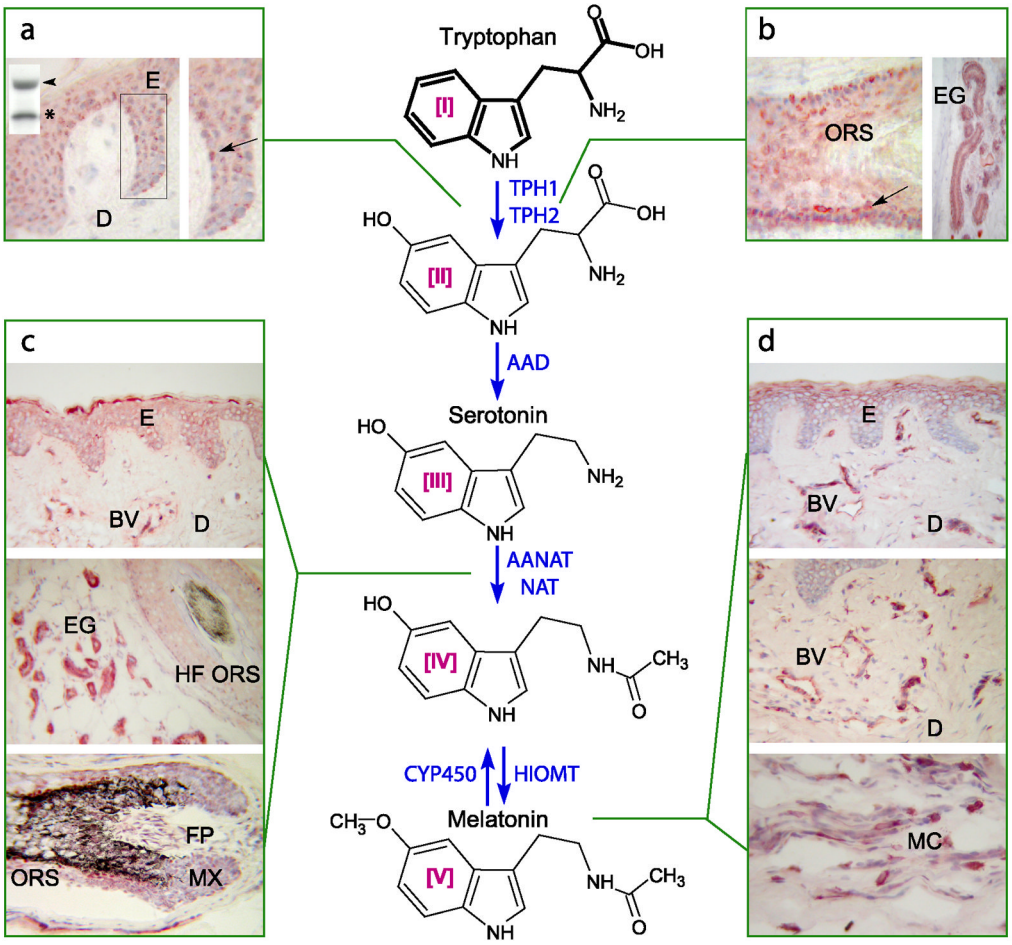

Figure 7. Melatoninegic system in the skin

TPH1 Western blot insert in the panel **a** is of approximately 50kD (arrowhead) that is processed and/or degraded to lower molecular weight species (asterisk). It is immunolocalized in the epidermis (ES), hair follicle (ORS), eccrine glands (EG), showing the highest expression in melanocytes (arrows) (panels **a** and **b**). 5-hydroxytryptophan is further decarboxylated by aromatic amino acid decarboxylase (AAD). AANAT (enzyme acetylating serotonin) is expressed in cells of epidermal, dermal and adnexal compartments (E, BV, EG and hair follicle structures in panel **c** on the left). Immunocytochemical localization of melatonin-like immunoreactivity is shown in panel **d** on the right (upper E, BV and MC). Immunocytochemistry was performed on human skin biopsies: E – epidermis, D – dermis, BV-blood vessel, EG - eccrine gland, HF ORS - hair follicle outer root sheath, FP – hair follicle papilla; MX – hair follicle matrix, MC – mast cells. For technical details see (Slominski et al., 2005d). Reproduced with permission from the publisher (Slominski et al., 2008a).

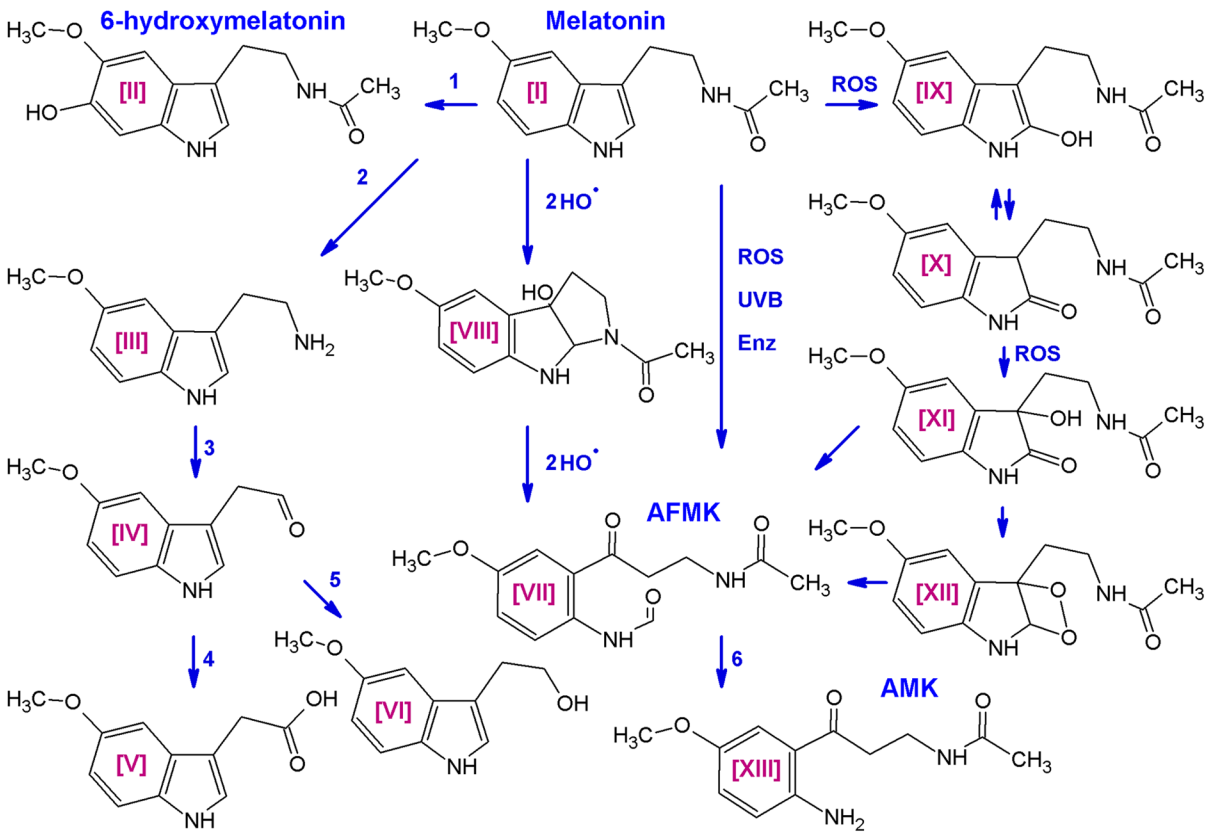

Figure 8. Pathways of melatonin degradation

The indolic pathway involves 6-hydroxylation of melatonin **[I]** by CYP1A1, CYP1A2 or CYP1B1 **(1)** to 6-hydroxymelatonin **[II]**. Melatonin deacetylase (**2**) produces 5-methoxytryptamine **[III]** that is oxidized by monoamine oxidase (**3**) to form 5-methoxyindoleacetaldehyde **[IV]**, which is converted to 5-methoxyindole acetic acid **[V]** by aldehyde dehydrogenase (**4**) or to 5-methoxytryptophol **[VI]** by alcohol dehydrogenase (**5**). In the kynuric pathway, melatonin can be converted non-enzymatically to N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK) **[VII]** in the process that may include generation of 3-hydroxymelatonin **[VIII],** 2-hydroxymelatonin **[IX]**, melatonin 2-indolinone **[X]**, 3-hydroxymelatonin 2-indolinone **[XI],** and melatonin dioxetane **[XII]** as intermediates. Enzymes or pseudoenzymes (Enz) are involved in melatonin conversion to AFMK. Different pathways can lead to the conversion of AFMK **[VII]** to AMK **[XIII]** (**6**). Reproduced with permission from the publisher (Slominski et al., 2008a).

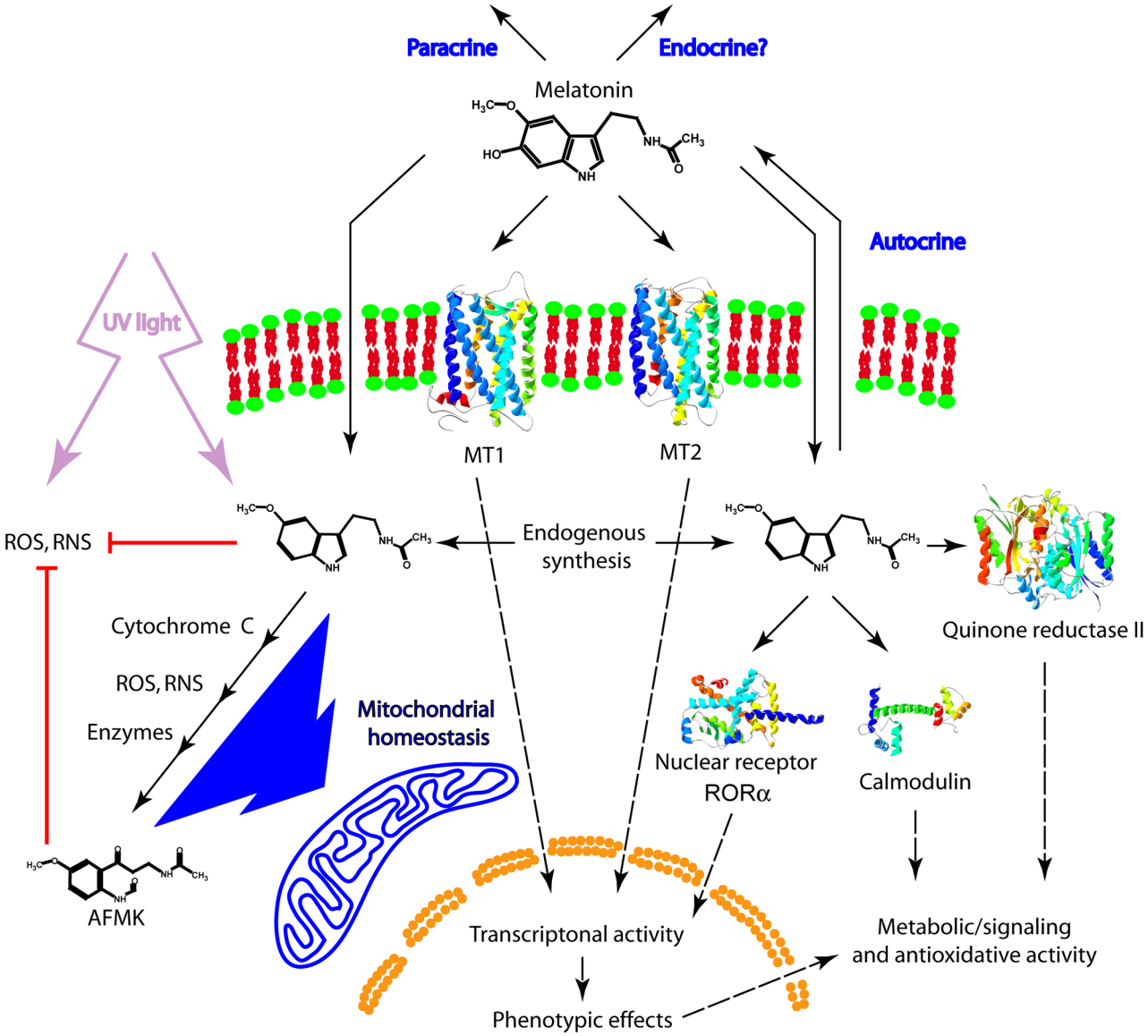

Figure 9. Phenotypic effects of melatonin in the skin

Exogenous or endogenously synthesized melatonin can regulate skin cell phenotype via interaction with melatonin receptors. Non-receptor actions are mediated via an interaction with intracellular proteins such as NQO2 or calmodulin. Melatonin and its metabolites can act as direct scavengers of reactive oxygen and nitrogen species (ROS and RNS) and affect mitochondrial functions. Direct effects are shown by solid lines and multiple reactions/ signaling are shown by dashed arrows lines. Reproduced from (Slominski et al., 2008a) with permission from the publisher.

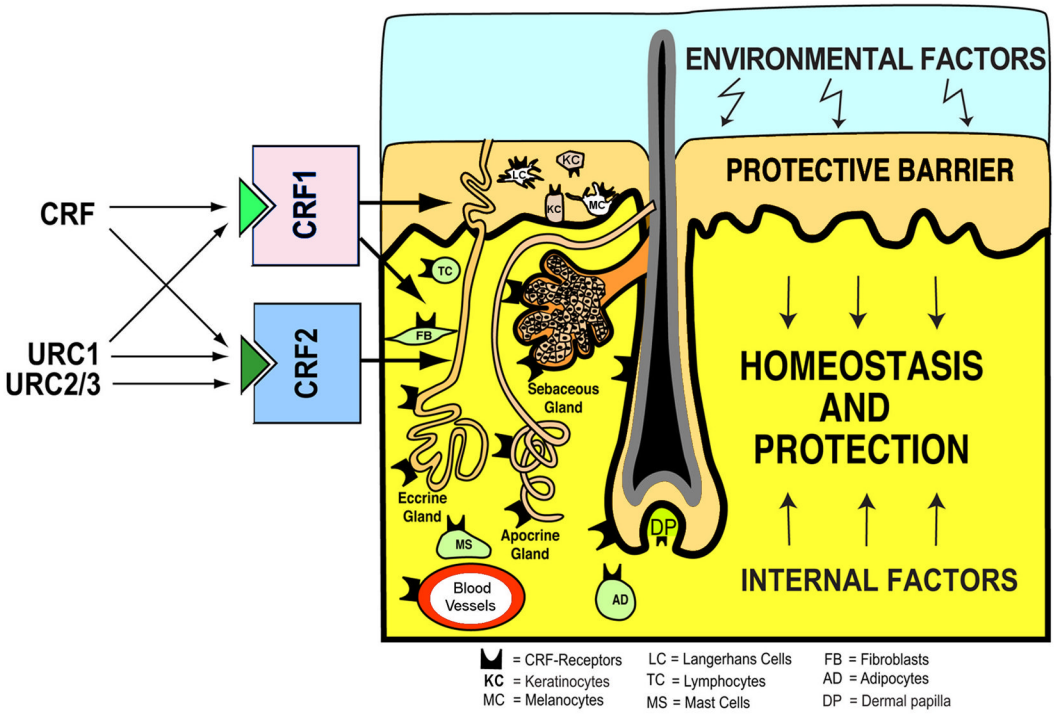

Figure 10.

CRF related signaling in the skin regulates protective and homeostatic functions of the skin. The specificity of the effect is defined either by local production of the molecule (CRF, Urc1, Urc2 or Urc3) or the type of the receptor expressed (CRF1 vs. CRF2). Reprinted from (Slominski, 2009b) with permission from the publisher

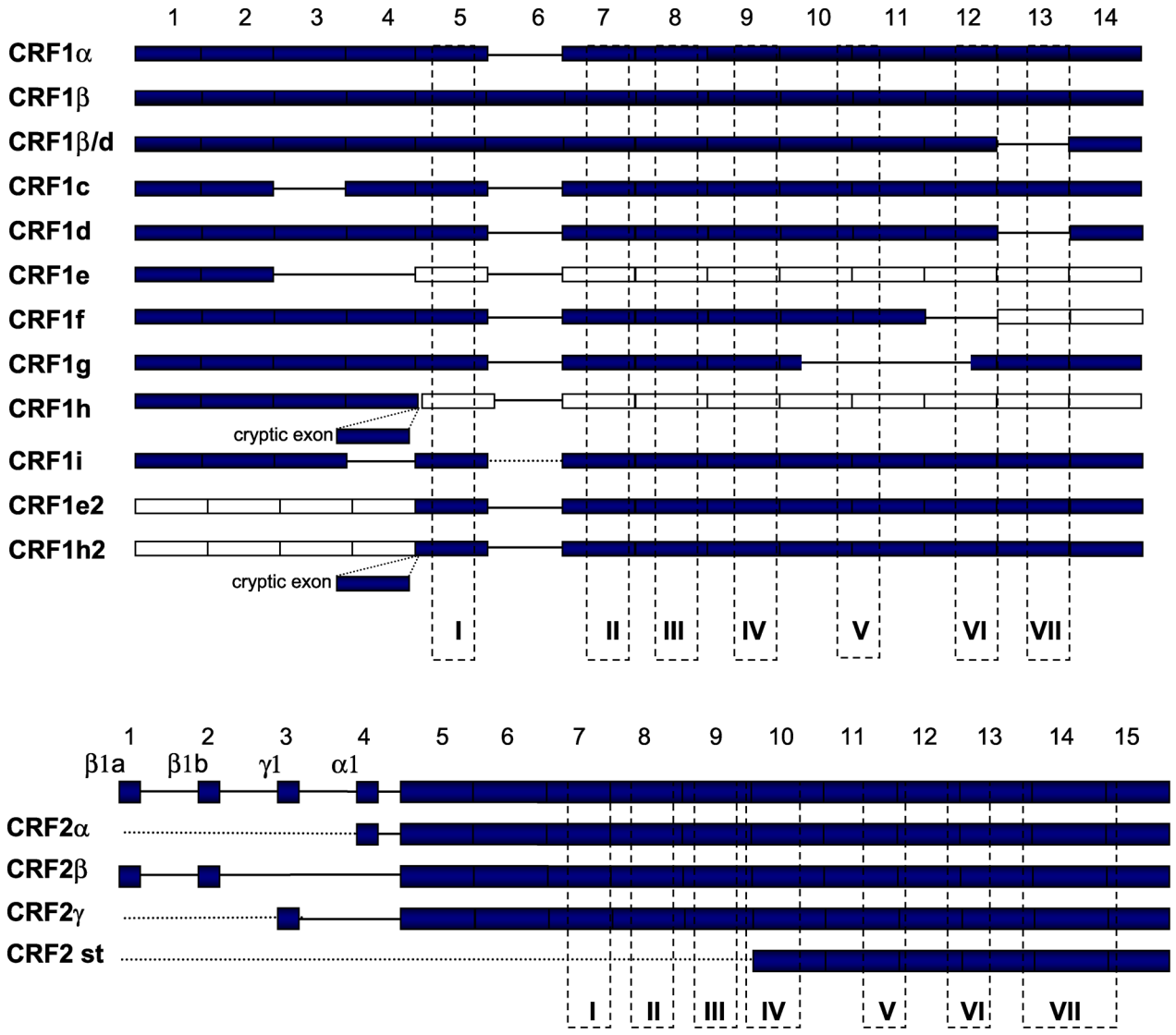

Figure 11. CRF1 and CFR2 receptors and their alternative splicing variants

Upper panel: Human CRF1 gene consists of 14 exons and due to alternative splicing at least ten isoforms can be generated with seven found in human skin (Pisarchik and Slominski, 2001, Slominski et al., 2006c). Coding exons are shown in blue and none coding exons due to frame shift followed by in-frame premature stop codon are showed as white squares.
Lower panel: CRF2 gene contains 15 exons and at least three alternative transcription start codons. Due to alternative splicing at least three main isoforms can be created (CRF1α, β, γ) and four additional isoforms could be synthesized from full length mRNA by employing alternative start codons (CRF2α1, β1a, β1b, γ1 as shown on the top of the panel).
Exon numbers are marked on the top of each panel. Transmembrane segments of 7TM are shown as squares (dashed line with number I to VII). See the text for appropriate citations.

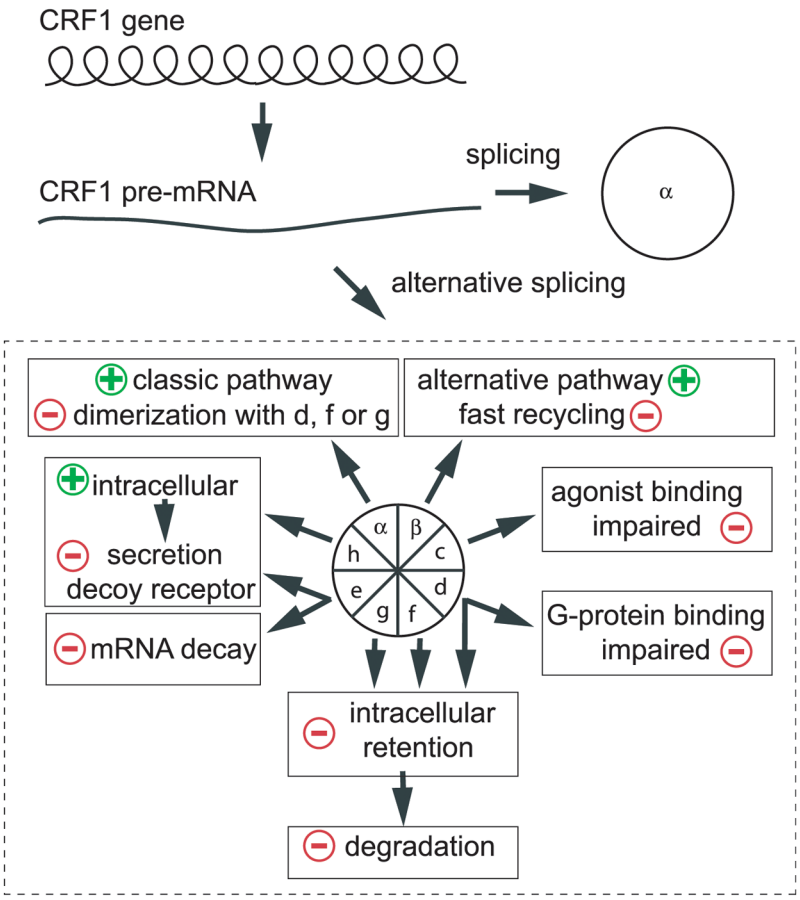

Figure 12. Regulation of CRF signaling by CRF1 isoforms

CRF1 gene contains 14 exons and only one isoform of receptor - CRF1β (also called pro-CRF1) is coded by all exons. CRF1 transcript is also subjected to alternative splicing resulting in at least 8 isoforms. Recent studies showed that expression and/or co-expression of CRF1 isoforms is responsible for modulation of CRF1 signaling mediated by main CRF1α or alternative CRF1β isoform. Soluble isoforms (CRF1e and h) were also found to stimulate CRF or modify Urc signaling when co-expressed with CRF1α. 'Minus' sign indicates inhibition of CRF signaling on different levels including: fast mRNA decay (CRF1e), dimerization and subsequent intercellular retention resulting in most probable premature receptor degradation (CRF1α with CRF1d, CRFf or CRFg), decoy receptor mechanism (CRF1h and e when secreted), agonist binding impairment (CRF1c) or G-protein binding inhibition (CRF1d). For details see (Zmijewski and Slominski, 2010a). Reproduced with permission from the publisher.

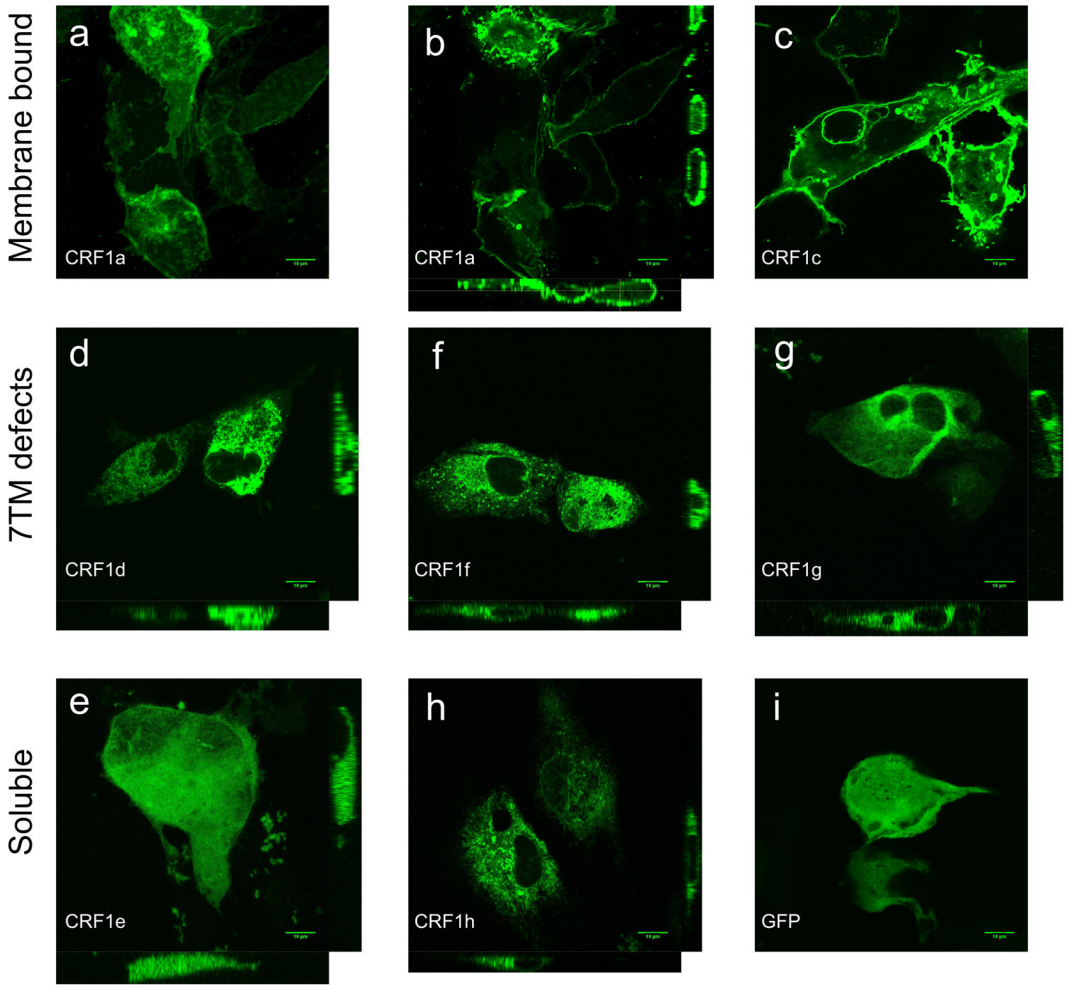

Figure 13.

Localization of the CRF1 isoform tagged with GFP in human adult ARPE-19 cells. Adult retinal pigment epithelium cells (ARPE-19) as alternative to melanocyte model of pigment producing cells showed similar intracellular distribution of the CRF1 isoform to that described previously in HaCaT keratinocytes (Zmijewski and Slominski, 2009b) and ATT-20 pituitary cells (Zmijewski and Slominski, 2009c). Isoforms CRF1α (Panels a and b) and CRF1c (Panel c) with full length 7-TM are found predominantly within cell membrane. CRF1 isoforms with defects (CRF1d – Panel d, CRF1f – Panel f, CRF1g – Panel g) within 7-TM region show intracellular localization. The soluble isoforms (CRF1e – Panel e, CRF1h – Panel h) are predominant inside the cells. The isoform CRF1e (Panel e) is the only isoform found inside the nucleus (similarly as GFP alone – Panel i). ARPE-19 were transfected with constructs caring CRF1 isoforms fused with GFP (Zmijewski and Slominski, 2009c) and images (as Z stacks) were collected with Zeiss LSM 510 laser scanning microscope (Zeiss, Germany). On the bottom and right sides of Panels b, d, f, g, e and h cross sections (from Z stacks) were shown to emphasize three-dimensional localization of CRF isoforms. On Panel a Z stack projection (average intensity) of APRE-19 cells overexpressing CRF1α is shown to emphasize presence of this isoform on the cell surface. The controls are represented by ARPE cells transfected with GFP alone (Panel i).

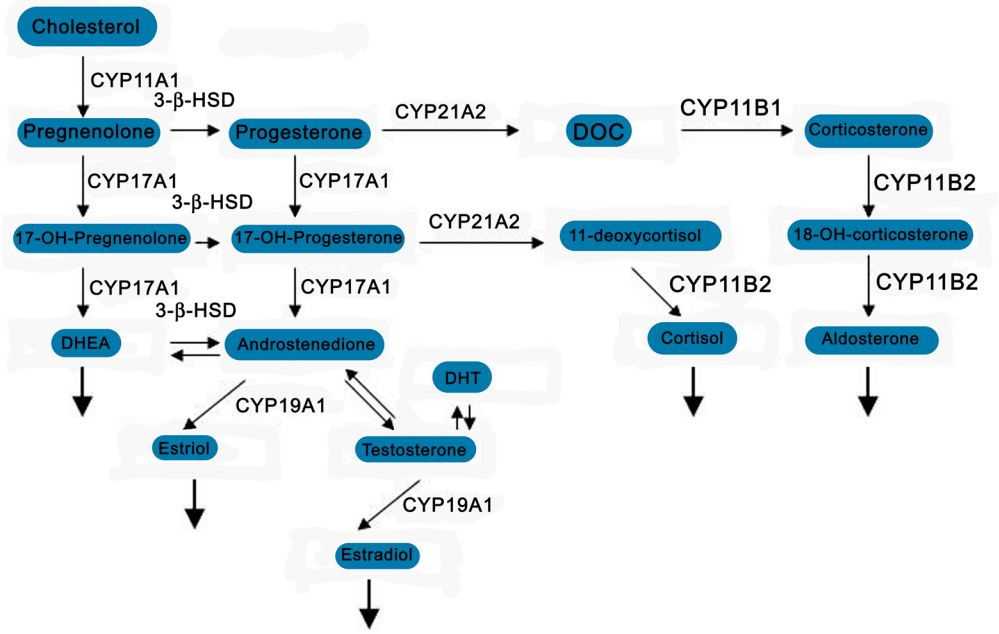

Figure 14.
Scheme of steroidogenic pathway.

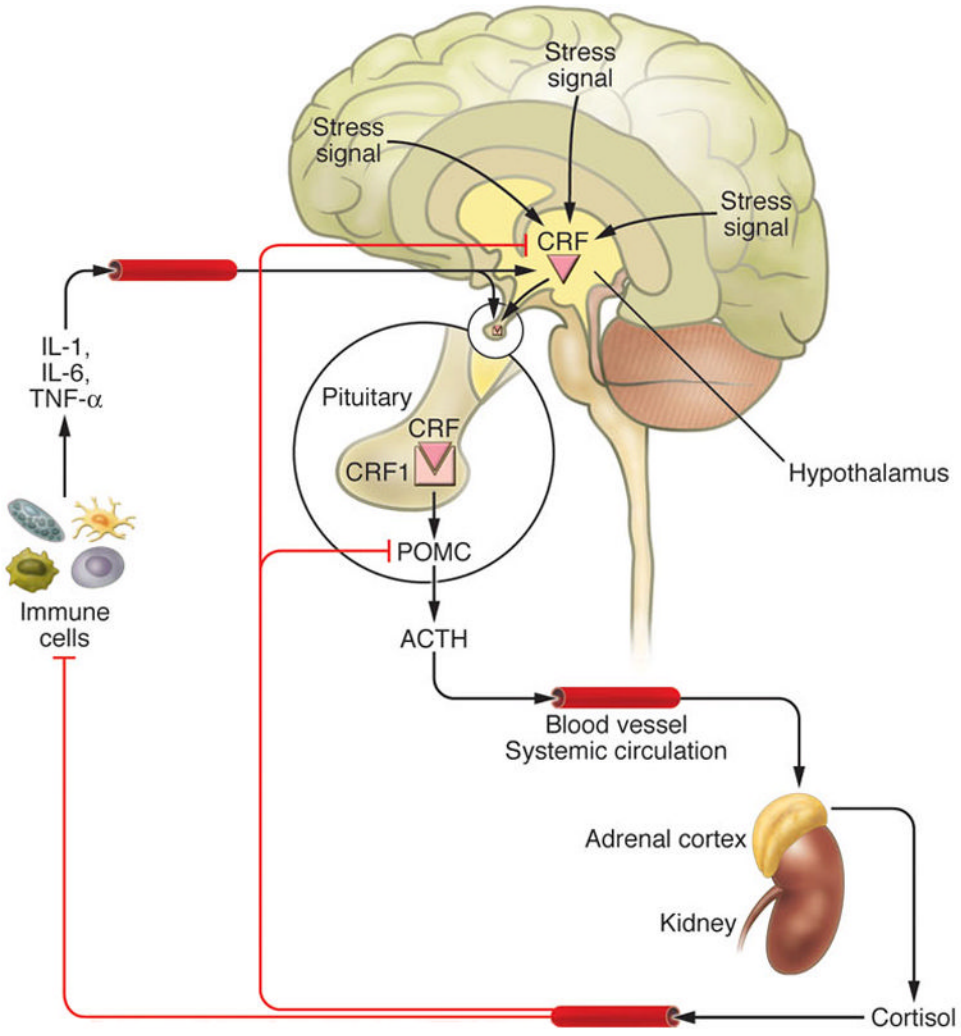

Figure 15. Organization of the systemic HPA axis
Modified from figure 1 published in (Slominski, 2007)

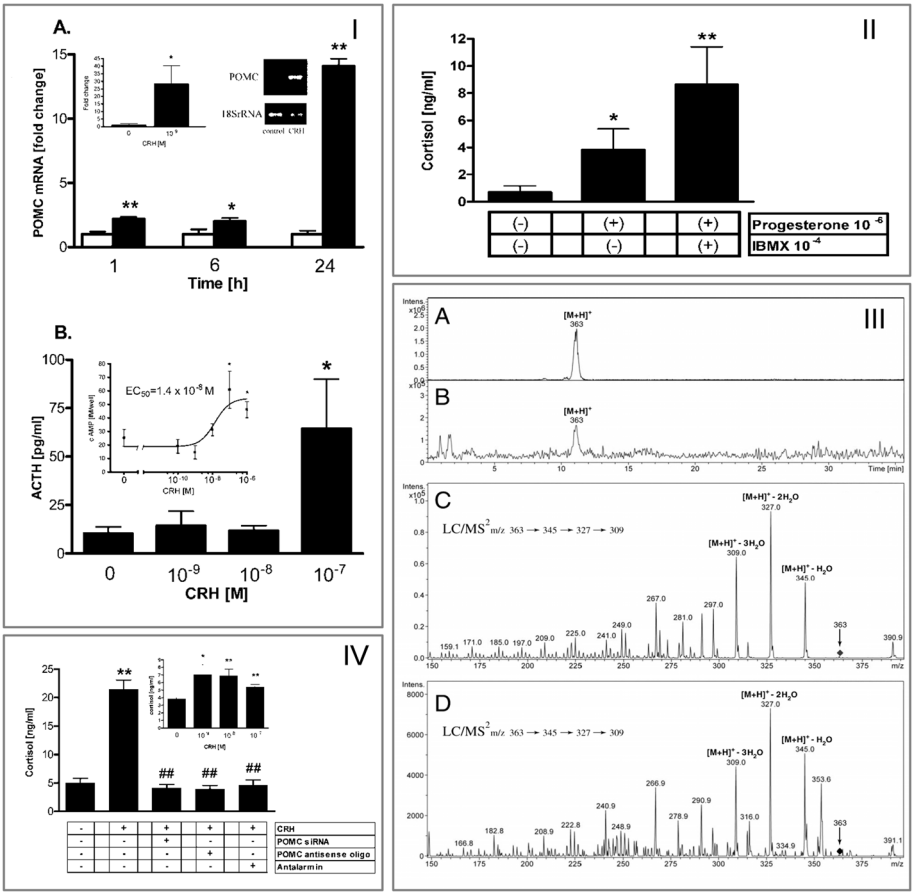

Figure 16. HPA algorithm is expressed in normal human melanocytes

A. CRH stimulates POMC gene expression, and ACTH production with attendant stimulation of cAMP.

B. Cortisol production is enhanced by addition of progesterone and/or IBMX (inhibitor of phosphodiesterase).

C. Cortisol is identified by LC/MS^2 in melanocytes (standard = A, C; conditioned media from melanocytes = B, D).

D. CRH stimulates cortisol production that is dependent on POMC expression and CRF1 signaling

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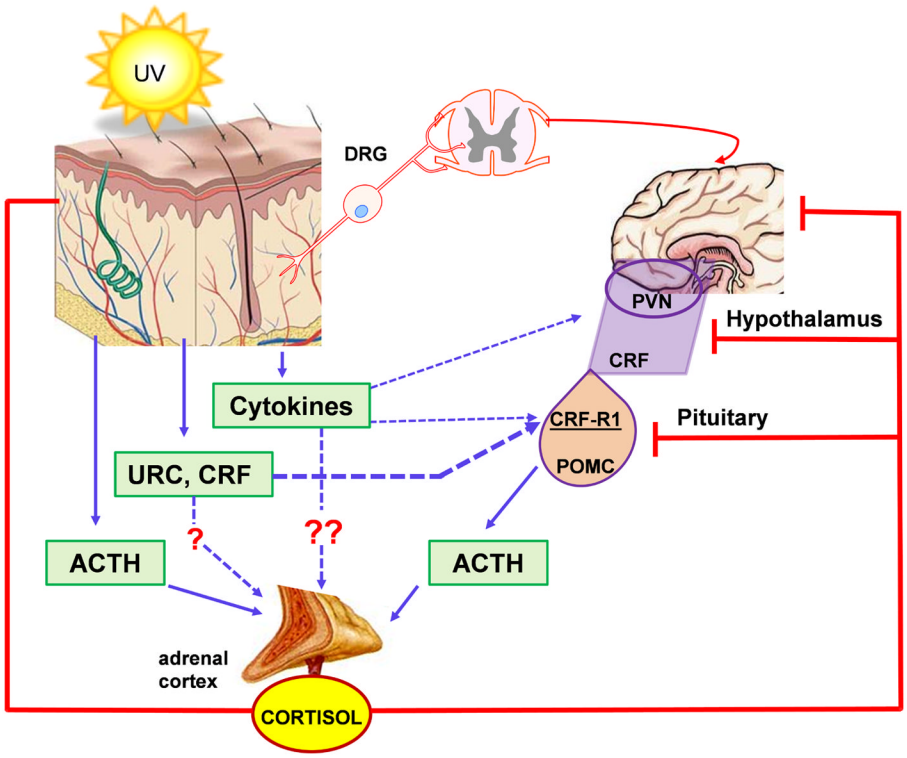

Figure 17. Skin stress response system can activate the central HPA with its direct homeostatic, metabolic and phenotypic consequences

We hypothesized that global responses (on the organism level) to UVR initiated in the skin and involving simultaneously activation of sensory receptors and local production of humoral messages (Slominski, 2005a, Slominski and Wortsman, 2000a, Slominski et al., 2008b). These signals are either delivered by ascending nerve routes to the brain or by circulation to hypothalamus to activate CRF production in the PVN; CRF then would enter portal circulation with subsequent activation of CRF1 in the pituitary. Skin humoral signals can also enter directly the pituitary from the circulation. The final outcome for these signaling processes is stimulation of ACTH release and of POMC activity. Alternatively, although less likely, the cutaneous factors can bypass this axis and enter adrenal gland directly from the circulation. The net effect of all of these processes is release of cortisol/corticosterone and induction of steroidogenesis with subsequent metabolic and homeostatic effects.

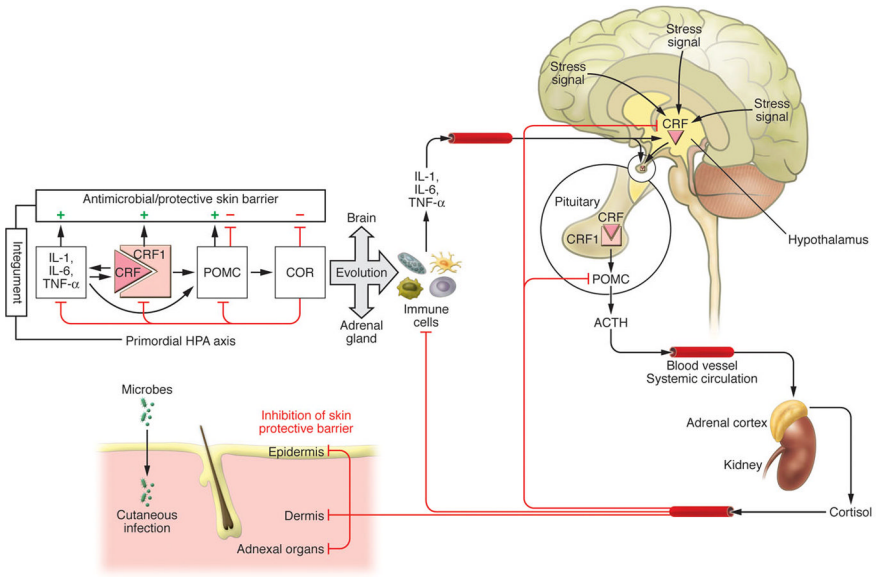

Figure 18. Proposed evolution of stress response system
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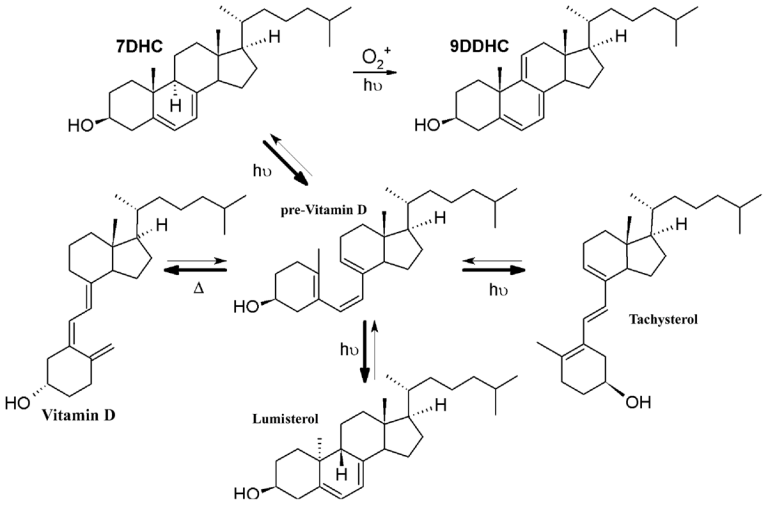

Figure 19. UVB induced production and transformation of 7-dehydrocholestrol
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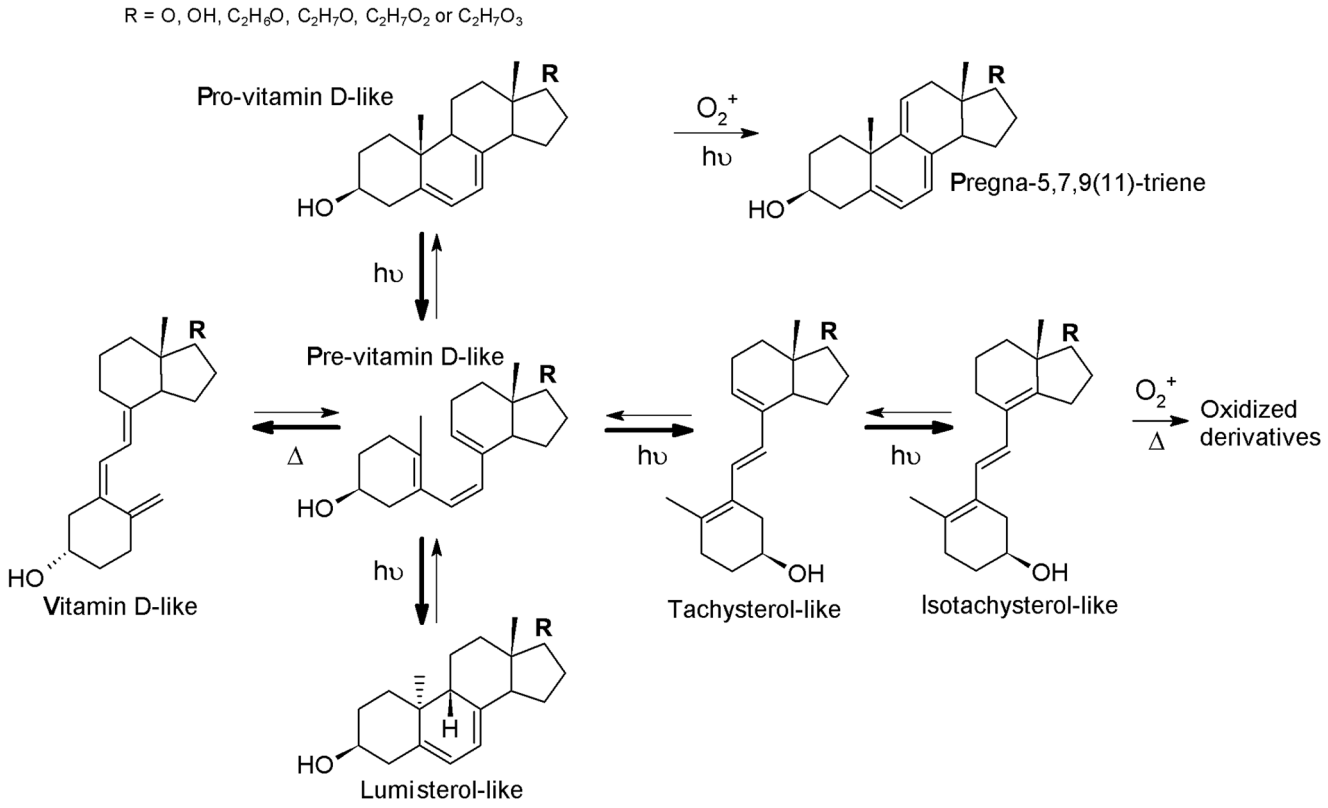

Figure 20.
UVB induced transformation of pregna- or androsta-steroidal 5,7-dienes. hν, Reprinted from (Slominski, 2009a) with permission from publisher

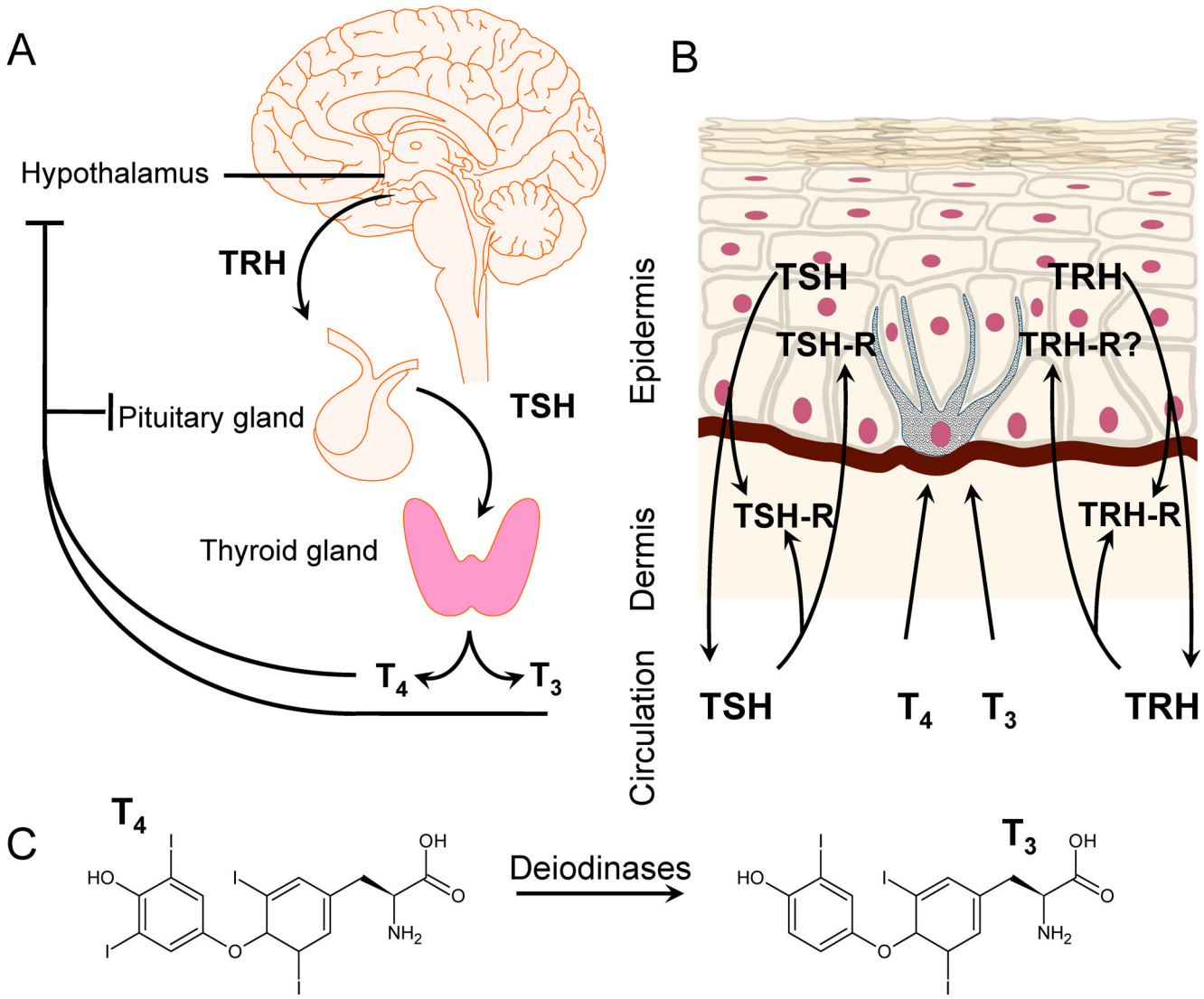

Figure 21.
Structure and functions of an equivalent of the hypothalamic-pituitary thyroid axis (HPT) in the skin.

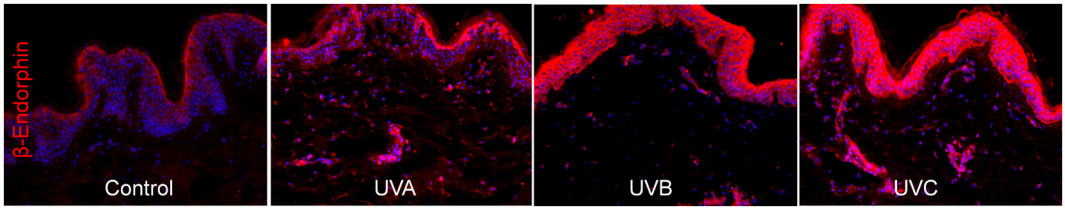

Figure 22.
Wavelength-dependent UV stimulation of β-END expression in epidermal layer of human skin. CY™3 positive (red) signals correspond to β-END immunoreactivity (methods described in Skobowiat et al., 2011).

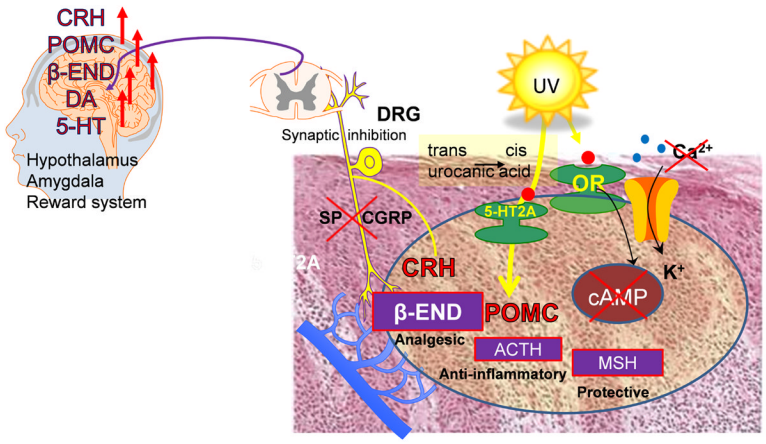

Figure 23.
Hypothetical pathway of addictive properties of the cutaneous neuroendocrine system induced by UV stimulation.