

Chapter 2

Biogenic Amines in the Skin

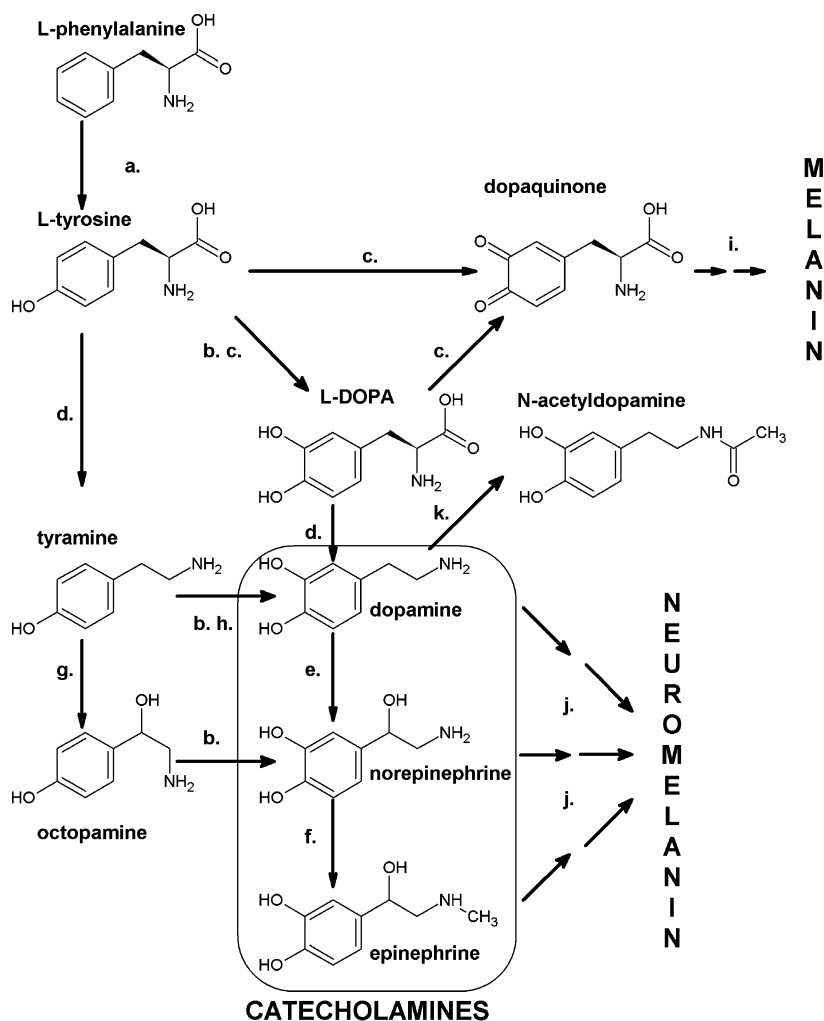
2.1 An Overview

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. 2008; Slominski et al. 2003d); however, non-receptor effects are also considered.

2.2 Catecholamines

2.2.1 Production and Metabolism

Nonessential 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 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) by either tyrosine hydroxylase (TH) or tyrosinase (Tyr), or decarboxylated to tyramine by L-amino acid decarboxylase (AAD) (Fig. 2.1). 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. 2.1). L-DOPA



- a. L-Phenylalanine hydroxylase
- b. Tyrosine hydroxylase
- c. Tyrosinase
- d. L-amino acid decarboxylase
- e. Dopamine β -monooxygenase

- f. Phenylethanolamine N-methyltransferase
- g. Dopamine β -hydroxylase
- h. Cytochrome P450 (Cyp2D)
- i. Melanogenesis
- j. Neuromelanogenesis
- k. Acetylation

Fig. 2.1 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

and catecholamines can also be oxidized by either 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. 2.1).

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. 2.2) (Fujiwara et al. 2005; Gillbro et al. 2004; Schallreuter et al. 1992, 1995). 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, 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. 1997, 1998). Furthermore, AAD activity requires pyridoxal phosphate (PP) as the cofactor, the cutaneous availability of which 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, 2011a). In fact, diffuse "melanocytic organ" can provide DOPA or its adducts to systemic circulation to serve either as a precursor for further modifications or as a bioregulator (Slominski et al. 1993a, 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

Fig. 2.1 (continued) 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 -hydroxylase to octopamine or dopamine, respectively. Octopamine could be metabolized to norepinephrine by TH. This alternative pathway which is present in invertebrates remains to be tested in the skin. Catecholamines also undergo oxidation to corresponding quinoinones with further multistep transformation to neuromelanin, a process similar to melanogenesis starting from L-DOPA

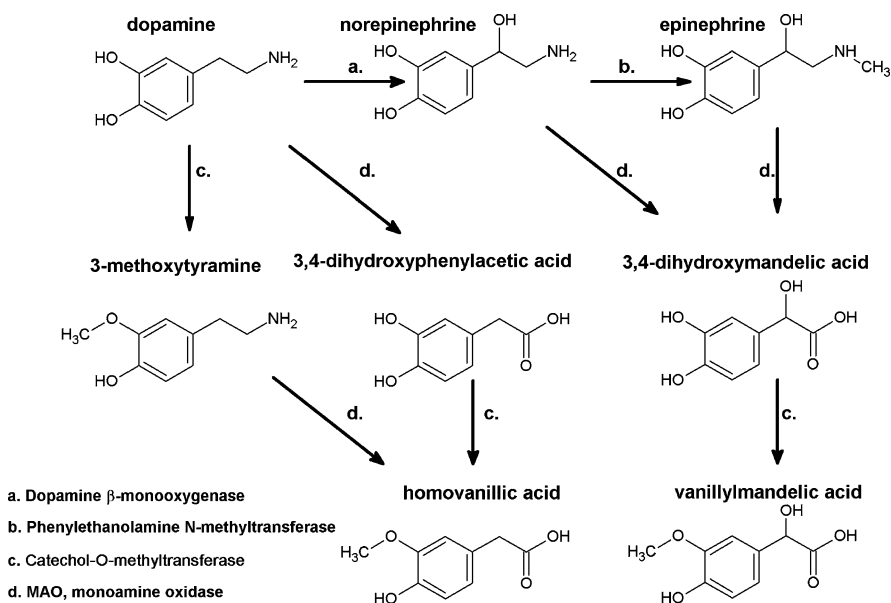


Fig. 2.2 Catecholamine catabolism. Catecholamines are deactivated by L-monoamine oxidase (MAO) and Catechol-*O*-methyltransferase (COMT) leading to the synthesis of homovanillic acid (from dopamine) or vanillylmandelic acid from norepinephrine or epinephrine. Alternatively, as shown for dopamine metabolism the order of reaction may be changes with COMT acting first and then followed by MAO

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, 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 1994). The D1-like receptor agonists stimulate G_s-dependent intracellular production of cAMP (Missale et al. 1998). The D2-like receptor agonists activate G_i proteins and inhibit intracellular cAMP signaling pathway (Missale et al. 1998; Watson 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 upregulates 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 α_1 and α_2 , and β receptors can be further subdivided into β_1 , β_2 , and β_3 subtypes. The α_1 (α_{1a} , α_{1b} , and α_{1d}) receptors couple to phospholipase C via $G_{q\alpha}$ and stimulate the formation of diacylglycerol and inositol trisphosphate (Cotecchia 2010). The α_2 (α_{2a} , α_{2b} , and α_{2c}) receptors couple to $G_{i\alpha}$ and inhibit the formation of cAMP, whereas β receptors are positively coupled to the formation of cAMP via $G_{s\alpha}$ (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 β_2 receptors and also α_1 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 toward 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- β_2 adrenergic system has been implicated in the pathogenesis of atopic dermatitis, psoriasis, and vitiligo (Sivamani et al. 2007). Expression of β_2 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 β_2 adrenoceptors in differentiating keratinocytes and with a defective calcium uptake in both keratinocytes and melanocytes (Schallreuter 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-Ezquerria 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 nonhuman systems (reviewed by Slominski et al. 2004c). Human melanocytes express α_1 and β_2 receptors (Gillbro et al. 2004; Hu 2000; Hu et al. 2000; Scarparo et al. 2000; Schallreuter et al. 1996). Activation of α_1 receptors leads to the IP3-DAG signaling (Schallreuter et al. 1996) and β_2 receptor activation leads to cAMP signaling (Gillbro et al. 2004). β_2 but not α_1 receptor activation induces pigmentation (Gillbro et al. 2004; Schallreuter et al. 1996). The expression of β_2 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 $\alpha 1$, $\beta 1$, and $\beta 2$ 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 $\beta 2$ 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 $\beta 2$ 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 $\beta 2$ receptors can also activate protein A kinase (PKA) which 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 $\beta 2$ 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 autooxidation 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, 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 (Scislawski et al. 1984, 1985). Also, diffusible products of DOPA oxidation are potent inhibitors of lipid peroxidation

(Memoli et al. 1997), and 5-S-cysteinyl-dopa 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 nonresident cells. Their phenotypic effects are mediated through activation of dopaminergic and adrenergic receptors, the expression of which is cell-type and cell-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. 1.1).

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 H₁ receptor is found on smooth muscle and endothelial cells and is responsible for smooth muscle contraction and decreased adhesion of endothelial cells. H₂ receptor is located on vascular smooth muscles and parietal cells in the stomach and is responsible for vasodilatation and gastric acid secretion. H₃ receptor is found in the central and peripheral nervous systems and is responsible for decreased secretion of several neurotransmitters including histamine, acetylcholine, serotonin, and norepinephrine. H₄ 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, H₁ and H₂ receptors are expressed on keratinocytes (Albanesi et al. 1998; Koizumi and Ohkawara 1999; Koizumi et al. 1998; Shinoda et al. 1998) and H₂ 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 H₂ 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, H₂ receptor signaling through the PLC second messenger system is inhibited during calcium-induced keratinocyte differentiation by an autocrine loop which involves downregulation of H₂ receptor expression and inhibition of histamine metabolism (Fitzsimons et al. 2002). In keratinocytes, activation of the H₁ receptor enhances UVB-induced IL-6 production (Koizumi and Ohkawara 1999; Koizumi et al. 1998), whereas H₁ receptor antagonists inhibit ICAM-1 expression (Ling et al. 2004). Histamine upregulates keratinocyte MMP-9 production via the H₁ receptor (Gschwandtner et al. 2008). H₂, however, not H₁, 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 C α and extracellular signal-regulated (ERK) kinase (Giustizieri et al. 2004; Kanda and Watanabe 2004). In cultured keratinocytes, histamine through the activation of H₁ receptor inhibits CCL17 production by suppressing p38 MAP kinase and NF- κ B 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 H₂ receptor, increases survival of keratinocytes acting by NF- κ B 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- κ B, 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 stimulating 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 upregulated in the B16F10 melanoma cells when compared to noncancerous melanocytes, which 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, which 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 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. 2011).

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-immuno-endocrine system of the skin (Slominski and Wortsman 2000) with local and systemic effects (Figs. 1.1 and 1.2).

2.4 Serotonergic System

2.4.1 *Production and Metabolism of Serotonin*

2.4.1.1 An Overview

Serotonin (5-hydroxytryptamine, 5-HT) is widely synthesized throughout the animal kingdom, plants, and unicellular organisms (Azmitia 2001, 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 enterochromaffin 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. 2008).

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 by either TPH1 gene expressed ubiquitously (Mockus and Vrana 1998) or TPH2 gene expressed predominantly in the brain (Zhang et al. 2004). This reaction requires oxygen and cofactor 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 1.2×10^{-5} M) and bound to serum albumins (ca. 6×10^{-5} M), with TPH having a K_m 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. 2008). 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 (5-HIAA), which is the main product of metabolism, or reduced to 5-hydroxytryptophol (HTOL) by alcohol dehydrogenase (E.C. 1.1.1.1) (Fig. 2.3). 5-HT can also be methylated to 5-methoxytryptamine (5MTT) and catabolized as shown in Fig. 2.3. Additional pathway involves serotonin acetylation by arylalkylamine *N*-acetyltransferase (AANAT) or arylamine *N*-acetyltransferase isoenzyme showing substrate specificity toward both arylamines and arylalkylamines to produce *N*-acetylserotonin (NAS)

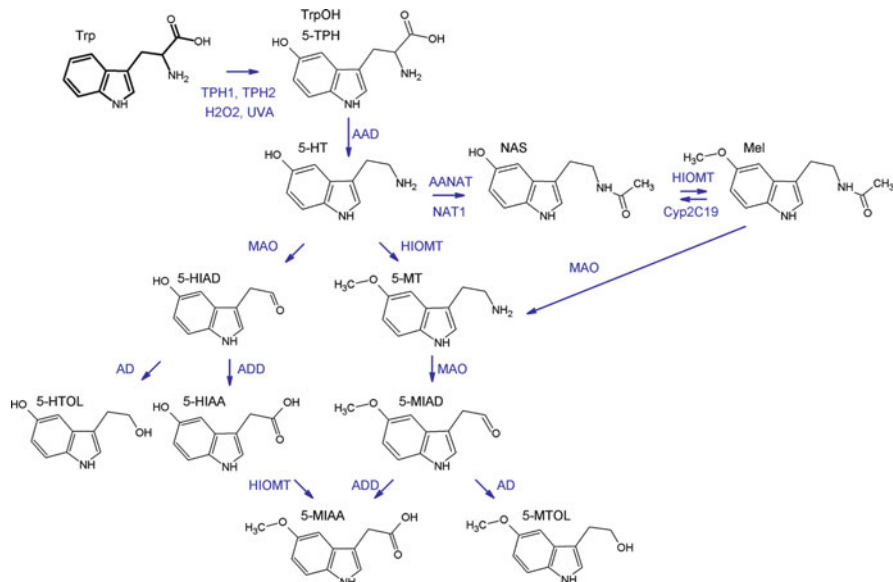


Fig. 2.3 Biochemical pathway of serotonin synthesis and metabolism in the skin. The pathway starts with hydroxylation of tryptophan by tryptophan hydroxylase type 1 or 2 (TPH1 or TPH2) to form 5-hydroxytryptophan (5-TPH; TrpOH). TrpOH can also be produced by nonenzymatic action of UVA and H_2O_2 . Serotonin (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 the formation of 5-hydroxyindoleacetaldehyde (5-HIAD) which is followed by the action of alcohol (AD) or aldehyde dehydrogenase (ADD) with the formation of 5-hydroxytryptophanol (5-HTOL) or 5-hydroxyindole-3-acetic acid (5-HIAA), respectively. Alternatively, HIOMT activity may also lead to the production of methylated derivatives of serotonin. The first step catalyzed by HIOMT leads to the formation of 5-methoxytryptamine 5-MT. The subsequent action of MAO results in 5-methoxyindoleacetaldehyde (5-MIAD) formation. Finally, AD or ADD facilitates the synthesis of 5-methoxytryptophol (5-MTOL) or 5-methoxyindole-3-acetic acid (5-MIAA), respectively. HIOMT was found also to catalyze the conversion of 5-HIAA to 5-MIAA. By the action of MAO melatonin can be metabolized to 5-methoxytryptamine (5-MT), thus entering the pathway leading to 5-MTOL or 5-MIAA formation

(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, the nature and mechanism of generation of which remain to be defined (Slominski et al. 2003b, c). After release into blood, serotonin is actively taken up into platelets and stored in solid granules with the help of a serotonin transporter (5-HTT), 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. 2008). Plasma serotonin is also cleared by the liver and lung endothelial cells and further catabolized to 5-HIAA.

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. 2.3). 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. 2002c, 2003b, c). 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. 2.4 and 2.5) (Slominski et al. 2003a, 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, c). 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, 2003b, c). Interestingly, the *TPH1* gene expression changes during murine hair cycle (Slominski et al. 2003b, c). In addition, TPH and serotonin are strongly expressed in rodent mast cells. It is also important to notice that the skin has a capability for de novo synthesis/recycling of the 6BH4 (Schallreuter et al. 1997, 1998, 2008a) and of pyridoxal 5'-phosphate (PLP) (Coburn et al. 2003) both serving as important cofactors necessary for the production of TrpOH and serotonin. Interestingly, nonenzymatic production of TrpOH through H₂O₂ and UVA radiation 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. 2.4 and 2.5) (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. 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 5-HIAA and/or 5-HTPOL (Slominski et al. 2003b, c). Similar metabolism was uncovered in rat skin, although in this species 5-HIAA was the

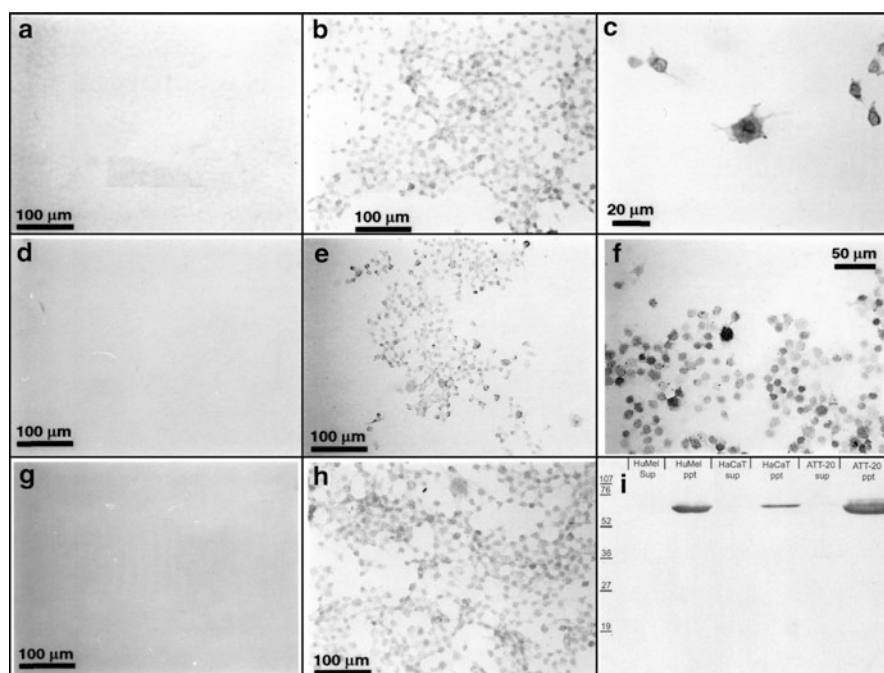


Fig. 2.4 Expression of TPH, serotonin (5-HT), and serotonin transporter (5-HTT) in skin cells. Panels **a–h** show immunocytochemical detection of 5-HT (**b, c**), 5-HTT (**e, f**), and TPH (**h**) in fixed cells using corresponding antibody at the dilution of 1:5,000 (antibody against 5-HT, Diasporin 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 cells. For technical details of the assays, see Slominski et al. (2005d)

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. 1990) and production of 5-HIAA 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 toward arylamines, and NAT-2 showing substrate specificity toward 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

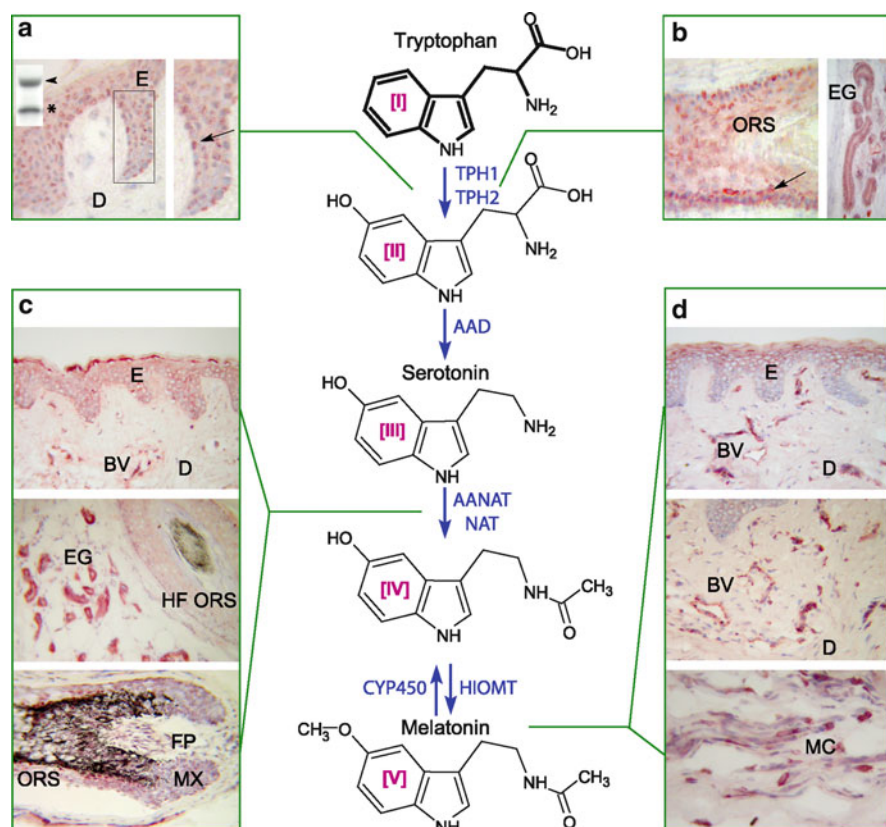


Fig. 2.5 Melanonegic system in the skin. TPH1 Western blot insert in the Panel **a** is of approximately 50 kDa (arrowhead) that is processed and/or degraded to lower molecular weight species (asterisk). It was immunolocalized in the epidermis (ES), hair follicle (ORS), eccrine glands (EG), showing the 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)

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. 1998), we detected cutaneous transformation of serotonin to NAS and, to a lesser extent, acetylation of tryptamine (Slominski et al. 2003b, c). 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 (the chemical nature of which remains to be defined) in a hair cycle-dependent fashion (Slominski et al. 2003b, c). 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 antioxidant or pro-oxidant (Azmitia 2007, 2010). The above functions are mediated through receptor-dependent and receptor-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 $G_{i\alpha}$ to inhibit cAMP formation while 5-HT4, 5-HT6, and 5-HT7 all couple via $G_{s\alpha}$ 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 $G_{q\alpha}$ 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-HT moduline is an allosteric modulator which regulates 5-HT5 receptor dimerization and formation of either homodimers or heterodimers. The receptors' heterogeneity and functional diversity are 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 the pattern of expression was cell type specific and modified by skin pathology (Slominski et al. 2003d). Interestingly, alternatively spliced form of *HTR2C* with a deletion of exon 2, a 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. 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-HT_{2A} gene in epidermal keratinocytes (Kaneko et al. 2009). However, these findings have to be considered with caution, since other researchers demonstrated that 5-HT_{2A} antagonists inhibited UVR-induced skin carcinogenesis (Sreevidya et al. 2008, 2010) and that sunlight-induced immunosuppression could be mediated via the activation of 5-HT_{2A} by cis-urocanic acid (Walterscheid et al. 2006). Furthermore, 5-HT_{2A} protein was detected by immunocytochemistry in dermal lymphocytes, fibrocytes, vasculature, and sensory nerve endings, abating the epidermis (Nordlind et al. 2008), while 5-HT_{1A} receptor was localized to keratinocytes of the upper epidermis, epidermal melanocytes, mast cells, and dermal vasculature (Nordlind et al. 2008). Furthermore, 5-HT_{1A} and 5-HT_{2A} 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-HT_{2C} 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-HT_{1A}, 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 were 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. 2.4). 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 and Pouyssegur 1990). 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 by Slominski et al. 2004b; 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. 1990; 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, the number of cells expressing both 5-HT_{1A} and tryptase diminishes, whereas the number of dermal cells expressing 5-HT_{2A} 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-HT_{2A} receptors. It is involved in the mast cell recruitment to the site of tissue injury through the activation of 5-HT_{1A}, however, without inducing their degranulation (Nordlind et al. 2008). Regulatory function of 5-HT_{1A} 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-HT_{1A} agonist, tandospirone, attenuates itching in patients with atopic dermatitis (Nordlind et al. 2008). On the other hand, treatment with 5-HT_{2A} 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 was 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-HT_{2A} receptors are partially responsible for mediating scratching in mice (Tachibana et al. 1990). Although neither 5-HT₂ nor 5-HT₃ appears 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-HT_{2A} 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 downregulation of 5-HT₃ expression (Nordlind et al. 2008; Slominski et al. 2005c).

2.4.4 Reception of Ultraviolet Light

The cutaneous serotonergic 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-HT_{2A} 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-HT_{2A} mediates immunosuppressive effects of UVR after binding of cis-UCA (Walterscheid et al. 2006). A role for 5-HT_{2A} in UVB-induced skin photocarcinogenesis was also suggested (Sreevidya et al. 2008, 2010). 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-HT_{2A} (Kaneko et al. 2009). Thus, there is sufficient information to support involvement of the local serotonergic 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 5-HT receptors including 5-HT_{1A}, 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 serotonergic 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. 1.1 and 1.2.

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