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The endocannabinoid system of the skin in health and disease: novel perspectives and therapeutic opportunities

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Abstract

The newly discovered endocannabinoid system (ECS; comprising the endogenous lipid mediators endocannabinoids present in virtually all tissues, their G-protein-coupled cannabinoid receptors, biosynthetic pathways and metabolizing enzymes) has been implicated in multiple regulatory functions both in health and disease. Recent studies have intriguingly suggested the existence of a functional ECS in the skin and implicated it in various biological processes (e.g. proliferation, growth, differentiation, apoptosis and cytokine, mediator or hormone production of various cell types of the skin and appendages, such as the hair follicle and sebaceous gland). It seems that the main physiological function of the cutaneous ECS is to constitutively control the proper and well-balanced proliferation, differentiation and survival, as well as immune competence and/or tolerance, of skin cells. The disruption of this delicate balance might facilitate the development of multiple pathological conditions and diseases of the skin (e.g. acne, seborrhea, allergic dermatitis, itch and pain, psoriasis, hair growth disorders, systemic sclerosis and cancer).

The skin as an emerging neuro-immuno-endocrine organ

The skin and its appendages establish a ‘passive’ physicochemical barrier against constant environmental challenges. However, a plethora of recent research has defined that the skin and its adnexal components (i.e. hair follicles, sebaceous and sweat glands) also function as ‘active’ neuro-immuno-endocrine organs [1] with (i) well-defined neuronal networks and related functions; (ii) a wide-array of constantly remodeling non-neuronal cells and ‘mini-organs’ (i.e. hair follicle, sebaceous gland); (iii) orchestrated immunological machinery for inflammatory and immunological mechanisms; (iv) the synthesis and release of numerous growth factors, vasoactive substances and hormones (Box 1).

Introduction to skin biology

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The skin is the largest organ of the integumentary system (the organ system that protects the body from damage) and is composed of multiple layers and cell types:

Epidermis

made of keratinocytes (which provide waterproofing and serve as a barrier to infection), Merkel cells (which function as mechanoreceptors for the sensation of touch and pressure), melanocytes (whose activity of melanogenesis defines skin color) and Langerhans cells (which function as professional antigen-presenting cells of the skin immune system). In addition, sensory nerve endings (recognizing e.g. touch, pressure, temperature as well as pain and itch) might also reach the lower layers of the epidermis.

Dermis

a dense connective tissue composed of collagen, elastic and reticular fibers produced mainly by dermal fibroblasts. In addition, the dermis is supplied by blood and lymphatic vessels and is highly innervated by both sensory afferent as well as motor efferent (which participate e.g. in vasoregulation) nerve fibers establishing a dense neuronal network. Of further importance, the dermis is the ‘home’ of the skin appendages such as the hair follicles as well as the sebaceous and sweat glands.

Hypodermis (or subcutis)

made of adipocytes, fibroblasts and macrophages (part of the skin immune system). In addition, the subcutis is well supplied by vessels and nerve fibers.

The skin layers and cell types form a complex, multicellular communications network, the proper function of which establish the physiological skin homeostasis. Selected functions of the skin involve:

Barrier functions

waterproof anatomical protection barrier against, for example, physical environmental challenges (e.g. UV, temperature), microbial invasion, allergens, chemical irritants and so on.

Sensory functions

sensation of heat and cold, touch, pressure, vibration as well as pain and itch (related to tissue injury); release of neuropeptides that regulate local vasoregulatory, immune-inflammatory and trophic functions.

Motor functions

vasoregulation (dilation or constriction of blood vessels) and piloerection.

Transport functions

transport of respiratory gases and nutrients between skin layers as well as from/to the skin surface; absorption of topically applied medications.

Exocrine functions

production and release (to the skin surface) of sweat and sebum, which exocrine products participate, for example, in thermoregulation, physical barrier formation, anti-microbial activity and so on.

Thermoregulatory functions

insulation by the subcuticular adipose tissue (actually, skin contains 50% of body fat); large cutaneous blood supply that enables precise control of direct heat losing mechanisms (i.e. radiation, convection and conduction); vasoregulation (vasodilation promotes heat loss

whereas vasoconstriction preserves body heat); evaporation (both insensible via skin pores and sensible via sweating); piloerection to further support insulation.

Endocrine functions

synthesis of a wide-array of hormones (e.g. vitamin D, steroids and peptide hormones) in multiple cutaneous cells; functional expression of hormone receptors as well as enzymes involved in the synthesis and metabolism of hormones; immune and inflammatory functions (a wide array of cutaneous immune-competent cells); synthesis and release of pro- and anti-inflammatory mediators (e.g. cytokines, chemokines and trophic factors) in almost all skin populations; anti-microbial activity of the sebum.

Regenerative functions

well-orchestrated and balanced proliferation, differentiation, survival and death 'programs' of the cutaneous cells and appendage structures, which enable life-long regeneration and regeneration of the skin; stem cell supply; wound healing.

For the delicate execution of cutaneous neuro-immuno-endocrine functions, the aforementioned components establish a complex, multicellular communication network [2, 3]. For example, activation of sensory neurons by various stimuli not only induces the antidromic (see Glossary) transmission of signals to the central nervous system but also results in the orthodromic release of certain neuropeptides (such as substance P and calcitonin-gene-related peptide) from the sensory afferents [4,5]. By contrast, these neuropeptides might then act on cutaneous non-neuronal cell types and exert local immuno-endocrine effects. Indeed, almost all skin cell populations (including those of the pilosebaceous unit) are capable of producing and releasing pro- and/or anti-inflammatory mediators that, by acting on neighboring cell types, can then fine-tune the overall immune response of the skin [1,3,5]. Similarly, production of numerous hormones by multiple cell types in the skin can exert local (paracrine or autocrine) regulation of cellular metabolism and functions of other cutaneous cell populations [1–5]. It is also important to note that the 'passive' (physico-chemical barrier) and 'active' (neuro-immuno-endocrine) functions of the skin and its appendages are strongly dependent on life-long regeneration and rejuvenation of cutaneous non-neuronal cells and mini-organs. These functions are defined by the well-orchestrated, delicate balance of cellular and organ proliferation and growth, survival and death, and regulated by a multitude of soluble mediators (e.g. growth and trophic factors, cytokines and chemokines) released from the skin cells [1–5].

Collectively, proper execution of the aforementioned mechanisms and the plasticity and pleiotropic nature of the cutaneous cells establish a solid base for physiological human skin homeostasis. Moreover, an appropriate equilibrium of cutaneous functions also enables the skin to protect the human body from constant environmental 'stressor' challenges such as microbial invasion, allergens, UV exposure and chemical irritation, among others. It is no wonder, therefore, that pathological alterations of cutaneous growth control and immuno-endocrine functions could lead to the development of multiple prevalent clinical conditions such as hyperproliferative skin diseases (e.g. psoriasis, tumors), hair growth disorders (e.g. alopecia, effluvium, hirsutism), acne vulgaris and atopic dermatitis [1–7].

In this article, the physiological regulatory function of the endocannabinoid system (ECS) in proliferation, differentiation, apoptosis and cytokine, mediator and hormone production of various cell types of the skin and appendages (e.g. hair follicle, sebaceous gland) are highlighted (Figure 1), and evidence on the putative involvement of the ECS in certain pathological conditions of the skin, such as allergic dermatitis, cutaneous itch and pain, and neoplastic cell growth, are discussed. Future preclinical and clinical research directions and

strategies to therapeutically target ECS for the management of various skin diseases are also envisioned.

The ECS and the skin

Identification of the main cannabinoid receptors (CB_1 and CB_2), their endogenous lipid ligands (endocannabinoids), biosynthetic pathways and metabolizing enzymes (collectively termed the ECS) [8–10], coupled with the discovery and/or rational design of numerous exogenous ligands for CB receptors [11], has triggered an exponential growth in studies exploring the continuously growing regulatory functions of this newly discovered physiological system both in health and disease [12–14].

Excitingly, modulating the activity of the ECS has turned out to hold tremendous therapeutic potential for a multitude of diseases and pathological conditions affecting humans [13,15,16], ranging from inflammatory [17], neurodegenerative [18–20], gastrointestinal [21,22], liver [23,24], cardiovascular disorders [25,26] and obesity [27,28], to ischemia/reperfusion injury [29], cancer [30] and pain [31].

The most extensively studied endocannabinoids are anandamide (*N*-arachidonoylethanolamine,AEA) and 2-arachidonoylglycerol (2-AG) [8,32]. Multiple pathways are involved in synthesis and cellular uptake of these lipid mediators; these are described in several excellent recent reviews [10,33,34] and beyond the scope of this article. The most common degradation pathways for AEA and 2-AG are the fatty acid amid hydrolase (FAAH) and monoacylglycerol lipase (MAGL) enzymes [10]. Endocannabinoids, similar to Δ^9-tetrahydrocannabinol (THC; the main active ingredient of the plant *Cannabis sativa*), predominantly exert their physiological effects via two main G-protein-coupled cannabinoid receptors; however, numerous additional signaling mechanisms and receptor systems (e.g. transient receptor potential cation channel, subfamily V, member 1; TRPV1) might also be involved [35]. Initially, the CB_1-mediated effects were described centrally and CB_1 receptors were thought to be restricted to the central nervous system, whereas CB_2 was first identified at the periphery in immune cells. Excitingly, findings over the past decade have clearly demonstrated that functional ECS is present almost in all peripheral organ systems [13–15].

Indeed, components of the ECS have also been discovered in the skin recently (Figure 1). Both CB_1 and CB_2 immunoreactivities were observed on numerous human and murine skin cell populations *in situ* such as on cutaneous nerve fibers, mast cells, epidermal keratinocytes and cells of the adnexal tissues [36–42]. Similarly, both CB_1 and CB_2 have been identified (at protein and mRNA levels) on cultured human primary (NHEK) and HaCaT keratinocytes [43–45]. Interestingly, in organ-cultured human hair follicles, exclusive expression of CB_1 was described [41], whereas CB_2 expression (unlike CB_1) was found on human sebaceous gland-derived SZ95 sebocytes [42]. AEA and 2-AG were detected in rodent skin [40,46], as well as in human organ-cultured hair follicles [41] and SZ95 sebocytes [42]. AEA, along with its transporter (AMT/EMT), synthetic and metabolizing enzymes (NAPE-PLD and FAAH) were also identified in cultured NHEK and HaCaT keratinocytes [43], and in murine epidermal cells/skin [40,47]. TRPV1, as key peripheral integrator of various sensory phenomena (e.g. pain, heat, itch), was originally described on nociceptive sensory neurons as a molecular target for capsaicin, the pungent vanilloid ingredient of hot chili peppers [48]. More recently, similar to $CB_{1/2}$, TRPV1 was also found on numerous non-neuronal cells types including human skin epidermal keratinocytes, dermal mast cells, Langerhans cells, sebocytes, sweat gland epithelium and various keratinocyte populations of the hair follicle [49–52]. TRPV1 might have important roles in skin health and in certain skin disorders, especially in ones associated with inflammation, pain and itch (e.g. in various types of dermatitis) [3–5,7]. However, the involvement of TRPV1-coupled signaling in the cellular actions of AEA on cell growth,

differentiation, proliferation and survival might exert marked cell-type specificity in the skin, and depending on the cell type it can be synergistic, antagonistic or independent from the $CB_{1/2}$ receptor stimulation [41,42,45,51,52]. The discussion of these complex effects is beyond the scope of this brief synopsis.

Role of the cutaneous ECS in skin growth control, survival and differentiation

Recent intriguing data suggest that the cutaneous ECS is fully functional (Figure 1). Indeed, as described later, the ECS has been implicated in the regulation of skin cell proliferation, survival and differentiation, the delicate balance of which is a key determinant of proper cutaneous homeostasis. Furthermore, fine-tuning of the endocannabinoid tone appears to be a key factor in modulating cutaneous growth and differentiation (Table 1).

Epidermis

Both phytocannabinoids and synthetic CB agonists inhibited proliferation of cultured transformed (HPV-16 E6/E7) human epidermal keratinocytes; yet, these effects were CB_1- and CB_2-independent [53]. On tumorigenic transformed murine keratinocytes (PDV.C57 and HaCa4), by contrast, the growth-inhibitory actions of synthetic CB agonists were prevented by both CB_1 and CB_2 antagonists [36]. It is also noteworthy that, on these latter mouse keratinocytes, the growth-inhibitory action of the cannabinoids was accompanied by CB_1- and CB_2-dependent apoptosis [36]. Interestingly, synthetic CB_1 and CB_2 agonists were ineffective in modulating cellular growth of both cultured NHEKs and non-tumorigenic human (HaCaT) and murine (MCA3D) keratinocytes [36].

By contrast, a recent study found that AEA markedly inhibited cellular growth and induced dose- and CB_1-dependent apoptosis in human HaCaT keratinocytes [45]. Consistently with this report, the ECS also regulates human epidermal differentiation, probably via CB_1-dependent mechanisms. Maccarrone *et al.* [43] have elegantly demonstrated that AEA, locally produced in the cells, inhibited the differentiation of cultured NHEK and HaCaT keratinocytes, as evidenced by the transcriptional downregulation of keratin 1, keratin 5, involucrin and transglutaminase-5 [44] and suppression of the formation of cornified envelopes. They have also shown that these effects were mediated by increasing DNA methylation through mitogen-activated protein kinase (MAPK)-dependent pathways (p38, p42/44) triggered by CB_1 activation [44]. Involvement of CB_1 in the regulation of epidermal differentiation is also suggested by the differential *in situ* expression of CB_1 in the human epidermis, being higher in the more differentiated (granular and spinous) layers [36,37].

Skin appendages

The pilosebaceous unit of the human skin, comprising the intimately localized hair follicle (HF) and the sebaceous gland (SG), can be regarded as the ‘brain’ of the skin because it controls a wide-array of the biological functions of this organ (from stem-cell supply through immunomodulation to cytokine production) [1–3]. Recent studies have suggested that the ECS might also have a regulatory role in the human pilosebaceous unit. Both human organ-cultured HFs and human SG-derived SZ95 sebocytes have been reported to produce AEA and 2-AG [41,42]. Furthermore, AEA and THC (but not 2-AG) dose-dependently inhibited hair shaft elongation and the proliferation of hair matrix keratinocytes. Cannabinoids also induced intraepithelial apoptosis and premature HF regression (characteristic signs of catagen transformation in the HF), processes that could be inhibited by a selective CB_1 antagonist. Because CB_1, unlike CB_2, is expressed in a hair-cycle-dependent manner in the human HF epithelium, these data support the idea that human HFs exploit a CB_1-mediated endocannabinoid signaling system that might act as an autocrine–paracrine negative regulator

of human hair growth. Consistently with this idea, a recent study has demonstrated that CB_1 receptor antagonists do, indeed, induce hair growth in mice [54].

Interestingly, differential CB_2-dependent regulation by endocannabinoids has been observed in human immortalized SZ95 sebocytes [42]. In accordance with these findings, SZ95 sebocytes predominantly express CB_2, suggesting that CB_2 is largely expressed in undifferentiated epithelial cells of the human SG *in situ* [37,42]. Both AEA and 2-AG enhanced lipid production and induced (chiefly apoptosis-driven) cell death, hallmarks of sebocyte differentiation and hence a model of holocrine sebum production [42] via CB_2-coupled signaling involving the MAPK pathway. Moreover, endocannabinoids also upregulated the expression of key genes involved in lipid synthesis (e.g. peroxisome proliferator-activated receptor [PPAR] transcription factors and some of their target genes). Because cells with 'silenced' CB_2 exhibited significantly suppressed basal lipid production, these results collectively suggest that human sebocytes utilize an autocrine–paracrine, endogenously (and probably constitutively) active, CB_2-mediated endocannabinoid signaling system for positively regulating lipid production and cell death.

Skin tumorigenesis

Accumulating recent evidence also implicates the ECS in the regulation of growth of skin cells *in vivo*. Casanova *et al.* [36] have demonstrated that various human skin tumors (e.g. basal cell carcinoma, squamous cell carcinoma) express both CB_1 and CB_2. Local administration of synthetic CB_1 and CB_2 agonists induced growth inhibition of malignant skin tumors generated by intradermal inoculation of tumorigenic PDV.C57 mouse keratinocytes into nude mice. This growth inhibition was accompanied by enhanced intra-tumor apoptosis and impaired tumor vascularization (altered blood vessel morphology, decreased expression of pro-angiogenic factors such as VEGF, placental growth factor and angiopoietin 2). Consistently, cannabinoids were also reported to inhibit the *in vivo* growth of melanomas that express CB_1 and CB_2 by decreasing growth, proliferation, angiogenesis and metastasis formation, while increasing apoptosis [39]. By contrast, a recent study of Zheng *et al.*. [55] suggested that CB receptors and the related signaling pathways might be involved in the promotion of *in vivo* skin carcinogenesis. Using CB_1/CB_2 double gene-deficient mice, Zheng *et al.* [55] demonstrated that an absence of CB_1 and CB_2 receptors resulted in a marked decrease in UVB-induced skin carcinogenesis. They also found that a marked attenuation of UVB-induced activation of MAPKs and nuclear factor-κB was also associated with CB_1 and CB_2 deficiency.

Collectively, these studies suggest that the cutaneous ECS, as in other organs, might act to tonically modulate cell growth, proliferation and death [30,56] (Figure 1).

Role of the cutaneous ECS in allergic, inflammatory and fibrotic functions

Since the original discovery of the CB_2 receptors in immune cells, much evidence using various CB receptor agonists and antagonists or compounds that enhance the levels of endocannabinoids by decreasing their metabolism suggest that the ECS has numerous important immune modulatory effects (e.g. suppression of production of various cytokines, chemokines, arachidonic acid-derived pro-inflammatory metabolites and nitric oxide) during inflammation [17]. Although some controversies do exist in the field, it is generally recognized that the ECS exerts protective functions in large number of acute and chronic inflammatory diseases [13,17].

A recent study by Karsak *et al.* [40] has suggested that the ECS exerts a protective role in allergic inflammation of the skin. Using an animal model for cutaneous contact (allergic) hypersensitivity, Karsak *et al.* [40] elegantly demonstrated that the skin level of endocannabinoids was increased in contact dermatitis. They also found that mice lacking both

CB_1 and CB_2 (or treated with antagonists of these receptors) displayed exacerbated allergic inflammatory response. The existence of the ECS-mediated protection was also supported by a reduced allergic response in the skin of FAAH-deficient mice, which have increased levels of the endocannabinioid AEA. Moreover, the skin inflammation was suppressed by locally administered THC [40]. Similarly, in a murine model of passive IgE-induced cutaneous anaphylaxis, both synthetic non-selective CB agonists and saturated *N*-acylethanolamine derivatives (homologues of *N*-palmitoyl ethanolamine, PEA) exerted marked anti-inflammatory properties *in vivo* [57]. Notably, PEA does not act directly at CB_1, CB_2 or TRPV1, but it can markedly augment the effects of AEA at these receptors [58,59] as well as directly activate PPARα [60].

By contrast, using different animal models for acute and chronic contact dermatitis, Oka *et al.* [61] reported elevated 2-AG levels in the diseased skin. The symptoms of skin inflammation were markedly attenuated by CB_2 (but not CB_1) antagonists [61]. Likewise, others using different animal models (Table 1) to induce allergic contact dermatitis reported a decrease in the cutaneous inflammation of CB_2-deficient mice [62], and similar suppression of the inflammatory response by orally administered CB_2 antagonists was also observed [62,63]. Consistently, Zheng *et al.* [55], using CB_1/CB_2 double gene-deficient mice, recently reported that CB receptors are involved not only in the promotion of *in vivo* skin carcinogenesis (see earlier) but also in the UVB-induced cutaneous inflammatory processes. The reasons for the conflicting data on the role of CB_1 and CB_2 in cutaneous allergic responses and tumorigenesis are not clear, but they could, in part, be explained by the differences in the experimental models used (Table 1) and by an emerging scenario, according to which in some physiological functions ‘too much’ endocannabinoid tone can be as bad as ‘too little’, and both ‘enhancers’ and ‘reducers’ might be useful for the same type of disorder depending on its phase or exact cause [14]. The use of CB_1 and/or CB_2 antagonists, which are also inverse agonists [11] (Table 1), might further complicate the interpretation of some of these findings.

In a recent study Akhmetshina *et al.* [64] have demonstrated that CB_2 knockout mice or controls treated with CB_2 antagonist were more sensitive to bleomycin-induced dermal fibrosis compared with wild types and exhibited increased dermal thickness and leukocyte counts in the lesional skin. The phenotype of knockouts was mimicked by transplantation of knockout bone marrow into control mice, whereas CB_2 knockouts transplanted with bone marrow from wide-type mice did not display an increased sensitivity to bleomycin-induced fibrosis, indicating that leukocyte expression of CB_2 critically influences experimental fibrosis [64]. Decreased dermal fibrosis and inflammation was observed upon treatment with the CB_2 agonist, suggesting a potential therapeutic utility of selective CB_2 agonists for the treatment of early inflammatory stages of systemic sclerosis.

Role of the ECS in cutaneous sensory functions: pain and itch

The ECS has a crucial role in central and peripheral processing, and in the control of such skin-derived sensory phenomena as pain and itch. Synthetic CB agonists and/or endocannabinoids exert potent analgesic effects in both humans and animals by activation of CB_1 and/or CB_2 and possibly other receptors (e.g. TRPV1) at sensory nerve terminals and/or inflammatory cells. However, the detailed discussion of these effects is beyond the scope of this article and we would like to refer readers to overviews on this subject [31,65–67].

Perspectives in the ECS-targeted management of skin diseases

The aformentioned preclinical data encourage one to systematically explore whether ECS-modulating drugs can be exploited in the management of common skin disorders. However, the pleiotropic nature and strong cell-type dependence of the cutaneous ECS-mediated functions will require careful judgment for patient selection and indications. In this section,

we review preliminary data and discuss the possible applications of ECS-targeted therapies (Figure 2; Table 2).

Psoriasis and skin tumors: aiming to increase ECS tone

Data showing that the cutaneous ECS tonically inhibits cell growth and angiogenesis and induces apoptosis in most of the skin cell types, and that both human non-melanoma and melanoma tumors express considerable amounts of CB_1 and CB_2 [36,39,41,42,45,53], now warrant proof-of-principle studies to test the therapeutic value of cannabinoid agonists in the clinical management of hyperproliferative skin disease (e.g. psoriasis, which is characterized by a highly accelerated turnover of epidermal keratinocyte proliferation) and skin tumors of various cutaneous cell origins. Furthermore, these interventions (as detailed later) might also suppress skin inflammation seen in psoriasis.

Hair growth disorders: aiming to increase or decrease ECS tone

The novel concept that human HFs are both targets and sources of endocannabinoids, which, via CB_1 establish an autocrine–paracrine system for negatively regulating hair growth, invites careful investigation of the growth-inhibitory effects of CB_1 agonists in the putative management of unwanted hair growth such as hirsutism. Likewise, future exploitation of CB_1-antagonist-based adjuvant treatment options in the clinical management of alopecia areata and effluvium is also of potential interest.

Acne and seborrhea

Acne and seborrhea, the most common dermatological diseases, are characterized by highly elevated lipid (sebum) production of the SGs. In light of the aforementioned data that CB_2 activation in the SG by locally produced endocannabinoids markedly enhances lipid synthesis [42], it is envisaged that those agents that suppress the local production of endocannabinoids (NAPE-PLD and/or DAGL inhibitors) in the diseased SG and/or inhibit CB_2 on the sebocytes (CB_2 antagonists) might have therapeutic values. Furthermore, transdermal penetration of cannabinoids is well established [68,69], raising the possibility that these agents could be efficiently applied topically to the skin in the form of a cream.

Dry skin and related conditions

Conversely, applications of formulations containing cannabinoids that stimulate CB_2 (CB2 agonists) in the SG, and/or augment the local production of endocannabinoids and/or inhibit their degradation (FAAH and/or MAGL inhibitors) in the SG might act as novel therapeutic tools in excessively dry skin by enhancing fat production in the SG (and, hence, might attract the interest of the cosmetics industry). It is important to note, however, that ideally these topical medications should contain such phyto- and/or synthetic ECS-acting substances that, on absorption to the blood, do not penetrate the brain and hence do not exert psychoactive effects. It is also noteworthy that skin dryness is a leading cause of and/or accompanied by other skin diseases and symptoms such as itching and dermatitis. Therefore, such cannabinoid-containing creams could also be beneficial under these conditions.

With respect to the possible treatment of itching, it is most promising that Stander *et al.* [65] have reported that topically applied emollient cream containing PEA markedly (>86%) reduced itching associated with dry skin. Therefore, it can be hypothesized that the fat-production-promoting actions of cannabinoids might, at least in part, contribute to the beneficial effects seen in these patients.

Dermatitis

Topical formulations that contain cannabinoid ligands (or that enhance the cutaneous ECS tone) could have therapeutic values in skin inflammations. Indeed, recently, a new drug containing PEA has been approved by the FDA for the treatment of dermatitis [70]. Moreover, a recent pilot study on 20 pediatric patients suffering from atopic dermatitis aimed to assess the efficacy and safety of the twice daily application of a topical emulsion containing 2% adelmidrol, a PEA analog. Excitingly, this study showed an 80% increase in symptom resolution [70,71].

Systemic sclerosis

A recent experimental study has suggested that CB_2 agonists could represent a promising approach for the treatment of early inflammatory stages of systemic sclerosis (scleroderma) [64].

Pain and itch

As detailed elsewhere, various cannabinoid agonists in addition to agents that increase the cutaneous levels of endocannabinoids have been effectively used in various models of pain and itch [13,31,65–67].

Conclusions and future directions in experimental and clinical research

Collectively, it seems that the main physiological function of the cutaneous ECS is to constitutively control the proper and well-balanced proliferation, differentiation and survival, as well as immune competence and/or tolerance, of skin cells. Pathological alterations in the activity of the fine-tuned cutaneous ECS might promote or lead to the development of certain skin diseases. Therefore, it is envisaged (this is also strongly supported by pilot studies) that the targeted manipulation of the ECS (aiming to normalize the unwanted skin cell growth, sebum production and skin inflammation) might be beneficial in a multitude of human skin diseases. However, to predict the real therapeutic potential and translate the exciting preclinical observations discussed earlier into clinical practice, numerous important questions should carefully be addressed (Box 2). Nevertheless, targeting the cutaneous ECS for therapeutic gain remains an intriguing and provocative possibility warranting future studies.

Outstanding questions

- Are all members of the ECS functionally expressed in the human skin and appendages?
- How do various endogenous mechanisms (e.g. hormones, cytokines) that were shown to be involved in the control of human skin homeostasis regulate the activity of ECS?
- Is there any crosstalk between the ECS and the endovanilloid system in the human skin?
- Is there any alteration in the expression levels and patterns of elements of the ECS in various human skin diseases?

Glossary

Acne vulgaris (or acne), a common, multi-etiological skin condition characterized by increased sebum production and inflammation of the sebaceous glands; acne can be induced and/or

aggravated, for example, by stress, endocrine conditions (adolescence), immune/inflammatory factors, bacterial infection of the skin, diet, and so on.

a (*N*-arachidonoylethanolamine) and 2-AG (2-arachidonoylglycerol), the two most studied endocannabinoids, which exert biological effects similar to marijuana via activation of two main cannabinoid receptors.

Alopecia, a type of pathological hair loss affecting mostly the scalp; most common forms of alopecia: universalis, areata, androgenetic.

Cannabinoid receptors, G-protein-coupled receptors that bind to and mediate the effects of cannabinoids.

Cannabinoids, as a broader definition, cannabinoids refer to a group of substances that are structurally related to Δ^9-tetrahydrocannabinol (THC), that bind to cannabinoid receptors, or that modulate the activity of the endocannabinoid system. Cannabinoids can be divided to various classes: 'phytocannabinoids' occuring in the cannabis plant; 'endogenous cannabinoids' produced in the body; and 'synthetic cannabinoids' chemically synthesized in a laboratory to target cannabinoid receptors and/or enzymes involved in the production or metabolism of endocannabinoids.

Dermatitis, a universal term describing inflammation of the skin; as most skin diseases, dermatitis can be induced by various factors such as, for example, allergens (allergic dermatitis), infections, eczema (atopic dermatitis), external compounds (contact dermatitis) and so on.

Effluvium (or telogen effluvium), a form of alopecia characterized by diffuse hair shedding.

Endocannabinoid system (ECS), it includes endocannabinoids, the enzymes involved in the biosynthesis or metabolism, and their two G-protein-coupled cannabinoid receptors, CB_1 and CB_2, which are present in virtually all tissues.

Endocannabinoids, bioactive lipid mediators produced in virtually all cell types and organs of the body, which exert biological effects similar to those of marijuana. The most extensively studied endocannabinoids are AEA and 2-AG.

Hair cycle, a life-long regeneration program of the hair follicles controlled by various factors; the hair cycle can be divided to three major phases: anagen (growth), catagen (regression or involution) and telogen (resting or quiescence).

Hirsutisms, is excessive and increased hair growth (especially in women) on body regions where the occurrence of hair normally is minimal or absent.

Orthodromic, antidromic, in a neuron, an orthodromic impulse (i.e. an action potential) runs along an axon in its normal direction, that is, away from the soma towards the axon ending. An antidromic impulse in an axon refers to conduction of the action potentials opposite to the normal, orthodromic direction (i.e. from the axon terminal to the soma).

Phytocannabinoids, cannabinoids that are isolated from the plant *Cannabis sativa*; the most known phytocannabinoid is THC and cannabidiol.

Pilosebaceous unit, consists of the hair shaft, the hair follicle, the sebaceous gland and the erector pili muscle, which causes the hair to stand up when it contracts.

Psoriasis, is a chronic, autoimmune skin disease that is characterized by epidermal hyperproliferation and skin inflammation.

Seborrhea (or seborrhoeic dermatitis), an inflammatory skin condition that particularly affects the sebaceous-gland-enriched areas of the skin; similar to acne, multiple factors are listed in its etiology.

Sebum, a lipid-enriched, oily exocrine product of the sebaceous glands; sebum has various function such as waterproof-barrier formation, anti-microbial activity, transport, thermoregulation and so on.

Systemic sclerosis (scleroderma), a chronic autoimmune disease characterized by diffuse fibrosis (accumulation of connective tissue), degenerative changes, and vascular abnormalities in the skin, joints and internal organs.

THC, the main active ingredient of the plant *Cannabis sativa*, which predominantly exerts its physiological effects via two main G-protein-coupled cannabinoid receptors.

TRPV1, transient receptor potential cation channel, subfamily V, member 1; also referred as vanilloid receptor 1 (VR1).

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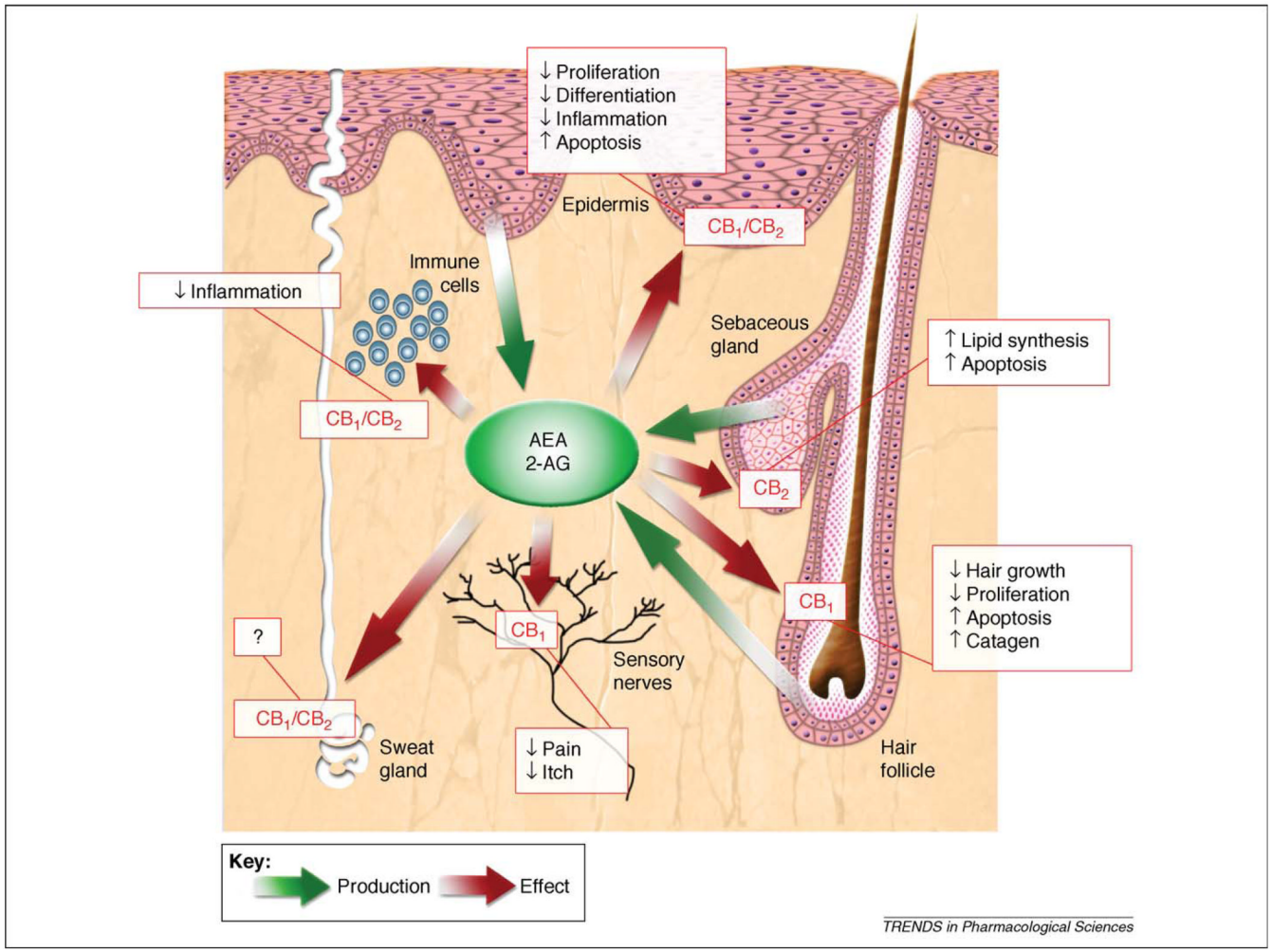

Figure 1.

Functions of the cutaneous ECS. Prototypic endocannabinoids such as anandamide (*N*-arachidonoylethanolamine; AEA) and 2-arachidonoylglycerol (2-AG) are produced locally in various cellular compartments of the skin (i.e. epidermis, sebaceous gland, hair follicle) (green arrows). These endocannabinoids, via binding to cannabinoid receptor subtypes 1 and/or 2 (CB_1/CB_2), constitutively control the proper and well-balanced cutaneous functions (e.g. sensation, growth, survival, immune competence and/or tolerance) (red arrows). For example, activation of CB_1 and CB_2 on epidermal keratinocytes by locally produced endocannabinoids results in the suppression of cellular proliferation, differentiation and the release of inflammatory mediators as well as the induction of apoptosis. Likewise, endocannabinoids, via CB_1/CB_2, inhibit inflammatory responses of resident and infiltrating immune cells. Furthermore, activation of CB_1 in the hair follicle by AEA attenuates hair shaft elongation and intrafollicular proliferation, whereas it stimulates apoptosis and the development of catagen regression. On another member of the pilosebaceous unit (i.e. on the sebaceous gland-derived sebocytes), locally released endocannabinoids markedly enhance lipid production and apoptosis via CB_2. Finally, skin-derived endocannabinoids inhibit various sensory phenomena (e.g. pain and itch) via CB_1 expressed on sensory afferent nerves.

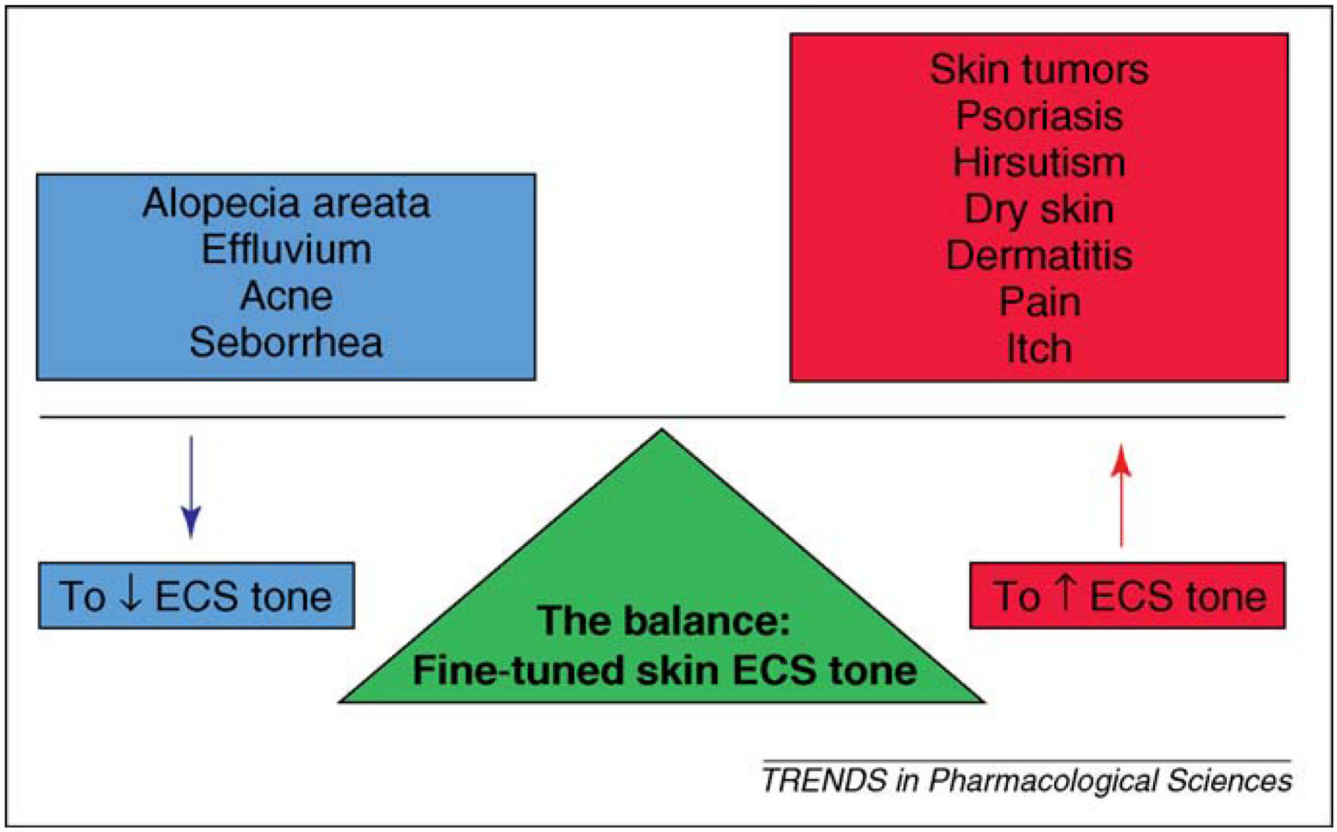

Figure 2.

ECS-targeted approaches in skin diseases. Modulations of the fine-tuned tone of the cutaneous endocannabinoid system (ECS) could have therapeutic values in the management of a large variety of human skin diseases. For example, suppression of the skin ECS tone (using e.g. CB antagonists and/or agents that attenuate the local production of endocannabinoids) could be used in the therapy of certain hair growth (e.g. forms of alopecia, effluvium) and sebaceous gland disorders (e.g. acne, seborrhea). Conversely, augmentation of the tone of the cutaneous ECS (using e.g. CB agonists and/or agents that stimulate the local production of endocannabinoids) could be beneficial in the treatment of various benign and malignant skin tumors, hyperproliferative skin diseases (e.g. psoriasis), excessive hair growth (e.g. hirsutism), different forms of dermatitis, dry skin conditions and sensory phenomena (e.g. pain, itch).

Table 1

Functions of the cutaneous ECS

Experimental system	Main findings	Pharmacological tools employed	Notes	Refs
***In vitro* cell and organ cultures**				
Human epidermal keratinocytes (NHEK, HaCaT)	CB_1 and CB_2 are expressed NAPE-PLD, AMT/EMT and FAAH are expressed AEA is produced AEA inhibits proliferation and induces apoptosis via CB_1 Synthetic cannabinoids do not affect proliferation AEA inhibits differentiation via CB_1	AEA, NADA: endocannabinoids WIN-55 212–2: mixed CB_1/CB_2 agonist JWH-133: selective CB_2 agonist SR141716A: selective CB_1 antagonist/inverse agonist SR144528: selective CB_2 antagonist/inverse agonist	CB_1 and CB_2 are expressed on human and mouse skin cell populations *in situ*	[36–45]
Human and murine transformed (tumorigenic) epidermal keratinocytes	Human: phyto- and synthetic cannabinoids inhibit proliferation (CB_1/CB_2 independent) Murine: synthetic cannabinoids inhibit proliferation and induce apoptosis via CB_1 and CB_2	HU210, WIN-55 212–2: mixed CB_1/CB_2 agonists JWH-015, JWH-133, BML-190: selective CB_2 agonists THC, cannabidiol, cannabinol and cannabigerol: phytocannabinoids SR141716A: selective CB_1 antagonist/inverse agonist SR144528: selective CB_2 antagonist/inverse agonist	Murine skin produces AEA and 2-AG, which express NAPE-PLD, AMT/EMT and FAAH	[36,47,53]
Human organ-cultured hair follicles	CB_1 is expressed AEA and 2-AG are produced AEA (unlike 2-AG) and THC inhibit hair shaft elongation and proliferation, and induce intraepithelial apoptosis and catagen regression via CB_1	AEA, 2-AG: endocannabinoids, mixed CB_1/CB_2 agonists THC: phytocannabinoid, mixed CB_1/CB_2 agonists AM-251: selective CB_1 antagonist/inverse agonist	CB_1 and CB_2 are expressed on human hair follicle *in situ*	[36,37,41]
Human sebaceous-gland-derived SZ95 sebocytes	CB_2 is expressed AEA and 2-AG are produced AEA and 2-AG stimulate lipid/sebum production and apoptosis via CB_2	AEA, 2-AG: mixed CB_1/CB_2 agonists ACEA: selective CB_1 agonists JWH-015: selective CB_2 agonists AM-251: selective CB_1 antagonist/inverse agonist AM-630: selective CB_2 antagonist/inverse agonist	CB_1 and CB_2 are expressed on human sebaceous gland *in situ*	[36,37,42]
***In vivo* animal models**				
Tumor induction in mice	Synthetic CB_1/CB_2 agonists inhibit tumor growth, angiogenesis and metastasis, and induce apoptosis in non-melanoma tumors and melanomas	THC: phytocannabinoid WIN-55 212–2: mixed CB_1/CB_2 agonist JWH-133: selective CB_2 agonist SR141716A: selective CB_1 antagonist/inverse agonist SR144528, AM-630: selective CB_2 antagonists/inverse agonist	Skin tumors (basal and squamous cell carcinomas, melanoma) express CB_1 and CB_2	[36,39]
Cutaneous contact allergic dermatitis	$CB_{1/2}$ double knockout mice display exacerbated allergic skin inflammation FAAH-deficient display reduced allergic response in the skin Locally administered CB antagonists exacerbate allergic inflammation Synthetic CB agonists and THC suppress inflammation	THC: phytocannabinoid HU210: mixed CB_1/CB_2 agonist HU308: selective CB_2 agonist SR141716A: selective CB_1 antagonist/inverse agonist SR144528: selective CB_2 antagonist/inverse agonist	Skin levels of endocannabinoids increase in contact dermatitis	[40]
IgE-induced cutaneous anaphylaxis	Synthetic CB agonists and PEA suppress inflammation	WIN-55 212–2, HU-210, CP 55 940: mixed CB_1/CB_2 agonists JWH-133: selective CB_2 agonist SR141716A, AM-281: selective CB_1 antagonists/inverse agonist SR144528, AM-630: selective CB_2 antagonists/inverse agonist		[57]
Acute and chronic contact dermatitis	CB_2 antagonist attenuates inflammation	2-AG: endocannabinoid, mixed CB_1/CB_2 agonists AM-251: selective CB_1 antagonist/inverse agonist	Skin level of 2-AG increases in contact dermatitis	[61]

Experimental system	Main findings	Pharmacological tools employed	Notes	Refs
		SR144528: selective CB_2 antagonists/inverse agonist		
Allergic contact dermatitis	CB_2 knockout mice display suppressed allergic skin inflammation Orally administered CB_2 antagonist attenuates inflammation	2-AG: endocannabinoid, mixed CB_1/CB_2 agonists HU308: selective CB_2 agonist SR144528, JTE-907: selective CB_2 antagonists/inverse agonists		[62,63]
UV-induced skin carcinogenesis and inflammation	$CB_{1/2}$ double knockout mice display attenuated UVB-induced skin carcinogenesis and inflammation	WIN-55 212–2: mixed CB_1/CB_2 agonist		[55]
Bleomycin-induced dermal fibrosis	CB_2 knockout mice display increased dermal fibrosis and inflammation CB_2 antagonist increased, agonist decreased the fibrosis and inflammation	AM-630: selective CB_2 antagonists/inverse agonist JWH-133: selective CB_2 agonist	Leukocyte expression of CB_2 critically influences experimental fibrosis	[64]

Abbreviations: 2-AG, 2-arachidonoylglycerol; AEA, arachidonoylethanolamide; AMT/EMT, anadamide/endocannabinoid membrane transporter; $CB_{1/2}$, type-1 and -2 cannabinoid receptor; FAAH, fatty acid amide hydrolase; IgE, immunoglobulin E; NADA, *N*-arachidonoyldopamine; NAPE, *N*-acylphosphatidylethanolamines; NAPE-PLD, NAPE-hydrolyzing phospholipase D; NHEK, normal human epidermal keratinocytes; PEA, *N*-palmitoylethanolamine; THC, Δ^9-tetrahydrocannabinol; UV, ultraviolet.

Table 2

Possible ECS-targeted approaches in skin diseases

Disease	Target cell population	Target receptor	Possible approach	Expected effects
Skin tumors	Transformed skin cell	CB_1 and CB_2	CB agonists or agents that increase ECS tone	Suppression of growth, angiogenesis and metastasis; induction of apoptosis
Psoriasis	Keratinocyte, immune cell	CB_1 and CB_2	CB agonists or agents that increase ECS tone	Suppression of keratinocyte proliferation and inflammation
Unwanted hair growth (e.g. hirsutism)	Hair follicle epithelium	CB_1	CB_1 agonists or agents that increase ECS tone	Suppression of hair growth, induction of intrafollicular apoptosis and catagen regression
Alopecia areata, effluvium	Hair follicle epithelium	CB_1	CB_1 antagonists or agents that decrease ECS tone	Stimulation of hair shaft elongation; suppression of intrafollicular apoptosis and catagen regression; induction of anagen
Acne, seborrhea	Sebaceous gland epithelium	CB_2	CB_2 antagonists or agents that decrease ECS tone	Inhibition of sebum/lipid production in the sebaceous gland
Dry skin	Sebaceous gland epithelium	CB_2	CB_2 agonists or agents that increase ECS tone	Stimulation of sebum/lipid production in the sebaceous gland
Dermatitis	Infiltrating immune cell, keratinocyte, sebocyte	CB_1 and CB_2	CB agonists or agents that increase ECS tone	Suppression of immune/inflammatory processes
Systemic sclerosis (scleroderma)	Infiltrating immune cells, fibroblasts	CB_2	CB_2 agonists or agents that increase ECS tone	Suppression of immune/inflammatory processes and fibrosis
Pain	Sensory neuron, keratinocyte, other skin cells	CB_1 and CB_2	CB agonists or agents that increase ECS tone	Suppression of release a algogenic substances; inhibition of transmission of signals in the nervous system
Itch	Sensory neurons, keratinocyte, sebocyte, other skin cells	CB_1 and CB_2	CB agonists or agents that increase ECS tone	Suppression of release a pruritogenic substances; inhibition of transmission of signals in the nervous system

$CB_{1/2}$, type-1 and -2 cannabinoid receptor; ECS, endocannabinoid system.