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REVIEW

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Recent advances in the endocrinology of the sebaceous gland

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ABSTRACT

The sebaceous gland, long considered an evolutionary relic with little-to-no physiological relevance in humans, has emerged in recent decades as a key orchestrator and contributor to many cutaneous functions. In addition to the classical physico-chemical barrier function of the skin against constant environmental challenges, a more novel, neuro-immune modulatory role has also emerged. As part of the complex intercellular communication network of the integumentary system, the sebaceous gland acts as a "relay station" in the skin for many endocrine factors. This review aims to offer a comprehensive overview of endocrine effects and subsequent interactions on this much maligned mini-organ.

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Introduction

The sebaceous gland, long considered an evolutionary relic with little-to-no physiological relevance in humans, has emerged as a key orchestrator and contributor to many cutaneous functions. These include the classical physico-chemical barrier function of the skin against constant environmental challenges, as well as more novel, neuro-immune modulatory roles and complex intercellular communication networks of the integumentary system. All of these processes are not only defined by local factors, but greatly influenced by the endocrine system. This review aims to offer a comprehensive overview of endocrine effects and interactions on this much maligned mini-organ.

The sebaceous gland – anatomy and functions

The sebaceous gland, comprised of sebocytes, is located in the dermis of the skin of all terrestrial mammals, primarily associated with hair follicles and the arrector pili muscles forming the pilosebaceous unit.[1,2] There is also great intra-individual variability in the distribution of sebaceous glands, since the density of the glands in various regions of the body is markedly different. The sebaceous gland differentiates in the embryonic stage between months 2 and 4 of gestation, with the rest of the pilosebaceous unit. During this process, a population of B lymphocyte-induced maturation protein 1 expressing unipotent stem cells is established,[3] which are responsible for regenerating the sebaceous gland in adult skin, although stem cells from the bulge region of the hair follicle may also act as a source of sebocytes.[4,5] The fully formed sebaceous gland found in adult skin may be divided into three zones, containing sebocytes in distinct stages of differentiation. The outermost *peripheral zone* contains the least differentiated, mitotically active population. These cells grow in size as they move centrally, differentiate, and accumulate lipid droplets, forming the *maturation zone*. As the final step of their differentiation sebocytes disintegrate and release their content via holocrine section in the *central necrosis zone*.[1,4] This continuous differentiation program is coordinated by a wide range of neural, paracrine, and endocrine mediators,[6] the latter of which is the main focus of this review.

The main function of the sebaceous gland is the holocrine production of sebum (tallow), the

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composition of which shows marked species specificity. Sebum is mostly composed of various neutral lipids (triglycerides, free fatty acids, wax esters, cholesterol and squalene), of which squalene and wax esters are unique and typical components. The main function of these secreted lipids is to cover the fur and the surface of the skin, and unsurprisingly they constitute the majority of skin surface lipids.[7-9] While sebum plays important roles in the impregnation of fur and thermal insulation as well as the production of pheromones in animals, these functions are mostly unrecognizable in humans, leading to the long-standing view that the human sebaceous gland is an evolutional relic.[10,11] This view has changed dramatically over more recent decades, since the composing lipids are important in skin barrier function, water resistance and protection from sunburn and UV radiation,[12-14] as well as in the establishment of the commensal bacterial flora of the skin.[13,15]

The sebaceous gland is not only notable as a producer of sebum, a structural constituent of the skin, but has other functions as well, most notably its contribution to the local immunological milieu. Sebocytes are capable of producing a wide range of (mainly pro-inflammatory) cytokines (interleukin [IL]-1α; IL1-β; IL-6; IL-8/CXCL-8 and tumor necrosis factor-α [TNFα]) and lipid-derived mediators.[16,17] The production of these factors is usually initiated by inflammatory factors, such as the presence of bacteria or certain endogenous mediators. *Propionibacterium acnes*, a known pathogenic factor in the development of acne, leads to the production of TNFα and IL-8/CXCL-8, while bacterial lipopolysaccharide (LPS) elevates IL-1α as well.[16] The endogenous inflammatory mediator arachidonic acid (AA) and the elevation intracellular calcium by the ionophore A23187 increased the release of IL-6 and −8.[17] Interestingly the activation of the calcium permeable channel, transient receptor potential vanilloid-1 (TRPV1) with capsaicin instead decreased the release of IL-1β.[18] AA-derived lipid mediators produced through the cyclooxygenase or lipoxygenase pathways (key enzymes of which are expressed on sebocytes) may also play a key role as inflammatory signals.[19] It is not just inflammatory mediators that can elicit these effects, but various hormones and neuropeptides including hypothalamic and pituitary hormones, i.e. corticotropin-releasing hormone (CRH) and α-melanocyte stimulating hormone (αMSH); for more detail see below in the relevant sections.

Sebaceous glands as sources and targets of sexual steroids

The link between sebaceous gland function and sexual steroids, most notably androgens, was established in the middle of the 20th century, more-or-less concurrently on animal models and humans.[20-24] Supporting these early forays into androgen effects on sebaceous physiology more recent works have proven the expression of androgen receptors both *in situ*[25,26] and *in vitro*[27] on human sebocytes. Androgens were also shown to increase the proliferation of sebocytes in culture,[27,28] although they can only stimulate the lipid synthesis of these cells in the presence of certain co-activators (e.g. linoleic acid, which stimulates peroxisome proliferator activated-receptors [PPARs]).[29,30] A more recent study has shown that *in vitro* models of the sebaceous gland lack androgen receptors (which may be found *in situ* on sebocytes), and that if reintroduced on these cells they are once again capable of responding to androgens without co-activators.[31] Further adding to the complexity of these results it was also reported in primary isolated sebocytes that the location of the sebaceous gland influences the effect of androgens; namely, these hormones were more effective in increasing the proliferation of facial sebocytes than on non-facial ones.[32-34]

The sebaceous gland appears to be much more than a target for androgens, however. These cells have been shown to express P450 side chain cleavage system which converts cholesterol to pregnenolone,[35] as well as multiple androgen metabolizing enzymes (3β-hydroxysteroid dehydrogenase/Δ5-4-isomerase, 17β-hydroxysteroid dehydrogenase [17β-HSD2], 5α-reductase-1, and 3β-hydroxysteroid dehydrogenase). They are also capable of synthesizing testosterone and of converting said testosterone into 5α-dihydrotestosterone (5α-DHT) which process, like lipid synthesis, was promoted by a simultaneous activation of PPARs.[36] An inverse correlation was also found between the expression of 17β-HSD2 and PPARγ in differentiated sebocytes *in situ*.[37] Conversely, sebocytes are also able to inactivate testosterone by converting it to

first androstenedione and then further to 5α-androstenedione.[27,38]

In contrast to the pro-lipogenic actions of androgens, estrogens were originally described to have opposite effects, namely to decrease the proliferation of sebocytes and to inhibit the production of sebum.[39,40] Patients with acne have also been shown to have lower serum estradiol and sex hormone binding globulin levels,[41,42] and combined oral contraceptive therapy has been shown to be beneficial in acne patients,[43] supporting the idea that estrogens decrease the function of the sebaceous gland. However, more recent reports have offered conflicting evidence, since whilst the expression of estrogen receptor –α and –β was described on sebaceous glands,[26] 17β-estradiol and progesterone had no discernable effect on either the proliferation or on the lipid production of SZ95 sebocytes.[44]

Role of hypothalamic-pituitary-adrenal (HPA) axis hormones in control of sebaceous glands

Sebocytes express ligands and receptors for a broad range of hormones of the hypothalamic-pituitary-adrenal gland axis. Corticotropin releasing hormone (CRH), the master regulator of the HPA axis, can target the CRH receptor-1 and 2 (CRHR1, CRHR2) expressed in sebocytes.[45,46] Beyond the receptors, sebaceous cells also express the CRH binding protein[46] which can negatively regulate the effect of CRH by binding and neutralizing it.[47] Supporting the functional role of the CRHRs in control of sebaceous functions, CRH (and to a lower extent urocortin, another CRHR agonist) was found to increase sebum production and inhibit proliferation, hallmarks of enhanced differentiation.[46,48] CRH was also found to stimulate IL-6 and IL-8 release[48] and increased mRNA expression of 3β-Hydroxysteroid dehydrogenase/Δ5-4 isomerase,[46] a key enzyme of steroid hormone synthesis. Moreover, CRH peptide and its mRNA was also detected in cultured sebocytes, suggesting a possible autocrine effect in the regulation of sebaceous functions.[46,48]

Hormones of the HPA axis downstream from CRH, as well as their receptors, were also detected in sebocytes. Proopiomelanocortin (POMC) and its derivatives, adrenocorticotropic hormone (corticotropin, ACTH), α- and β melanocyte stimulating hormone (melanocortin, MSH), and β-endorphin were described in sebocytes, as well as prohormone convertase enzymes which are responsible for the enzymatic cleavage of POMC.[49-51] Several receptors of the αMSH and ACTH, i.e. melanocortin receptor-1, 2 and 5 (MC-1R, MC-5R) are also expressed in sebocytes with a functional role in the control of sebaceous differentiation and lipid synthesis. Indeed, MSH and ACTH treatment induced differentiation and lipogenesis and decreased IL-1β induced IL-8 secretion. Suggesting its specific role, MC-5R was found only in differentiated sebocytes and characterized as a potential differentiation marker in sebaceous glands.[52-54] Moreover, μ-opioid receptors were also reported in sebocytes and β-endorphin was suggested to stimulate lipogenesis.[55]

The expression of the HPA axis in sebaceous glands suggests the presence of a local endocrine "stress axis", which might be involved in cutaneous/sebaceous stress responses. This hypothesis is supported by findings that CRH expression was elevated in sebaceous glands of acne affected skin[56] and upregulated in aged skin.[57] Like CRH, MC-1R also showed an increased expression in acne-affected skin.[58]

Growth hormones controlling sebaceous glands

Growth factors and hormones promoting growth have been extensively shown to influence sebaceous gland functions. Most notably the overproduction of growth hormone (GH) is commonly associated with "oily skin". In accordance with these results it was shown that GH receptors are not only expressed in skin,[59] but more specifically in the sebaceous glands *in situ*.[60,61] Supporting the functional effect of GH, it was shown that the hormone accelerated the differentiation of sebocytes in a rat preputial model, while having little effect on their proliferation. This is in contrast to insulin-like growth factor 1 (IGF-1), which mainly affected proliferation of the cells. Insulin, the "universal growth hormone" stimulated both proliferation and differentiation as well as augmenting the above mentioned effects of GH, IGF-1 and 5α-DHT.[62] In human *in vitro* models, IGF-1 and GH had similar effects, with IGF-1 being the more efficacious of the two,[44] acting through the PI-3-kinase/Akt/sterol response element-binding protein-1 (SREBP1) pathway.[63,64] Further supporting the role of this axis in the pathogenesis of acne it was recently shown that IGF-1 also increases the production of inflammatory

cytokines and sebum from cultured primary human sebocytes and the commonly used cell line SZ95.[65,66]

Epidermal growth factor (EGF), a more "local" growth hormone may also have direct effects on sebocytes, which express its receptor (EGFR).[67] In human *in vitro* systems EGF inhibits differentiation, which coincides with the observation that one of the reported side effects of EGFR inhibitor antibody (cetuximab) treatment are acneiform eruptions.[68] These findings further highlight the inadequacy of animal models in studying sebocyte biology, since in hamster sebaceous glands EGF increased the number of cells.[69] Interestingly, a more recent paper has shown that cetuximab does not induce inflammatory mediator release from *in vitro* cultured sebocytes, while it does increase their lipogenesis.[70,71] This hints at the possibility that a more complex signaling network is responsible for the aforementioned lesions. Besides EGF, the role of fibroblast growth factor receptor-2b (FGFR2b) coupled signaling in the control of sebaceous functions and the development of acne has also been proposed.[72,73]

Central role of sebocytes in the cutaneous endocannabinoid system

As detailed above, several systemic hormones regulate local cutaneous lipid homeostasis, controlling sebaceous lipid, and paracrine/endocrine mediator production. However, sebaceous glands are not only sources of lipids, but also stand under the control of locally produced lipid mediators among which endocannabinoids (ECs) emerge.[74] ECs, sharing molecular targets with the active ingredients of the plant *Cannabis sativa*, are locally produced arachidonic acid derivatives which activates, among else, G protein-coupled cannabinoid receptors CB_1 and CB_2. These endogenous mediators, their receptors and the enzymatic system involved in their synthesis and metabolism form the endocannabinoid system (ECS), a powerful regulatory network virtually presented in all tissues.[75] In the skin, similar to other organs, an EC tone is established by the regulated production and degradation of the ECs among which the most studied ones are the arachidonoylethanolamine (anandamide or AEA) and 2-arachidonoylglycerol (2-AG).[74] Both AEA and 2-AG are produced by epidermal keratinocytes[76] hair follicles[77] and sebocytes,[78] as well. The established EC tone is not only analgesic limiting neural excitation at the sensory terminals,[79,80] but it may exert anti-inflammatory, immunosuppressive, anti-allergic and itch inhibiting effect.[81,82] Moreover, ECs induce apoptosis of epidermal keratinocytes,[83] modulate their differentiation and barrier formation[76,84] and inhibit hair growth.[77]

Human sebaceous glands and cultured sebocytes express CB_2 which mediates the lipogenic effect of endocannabinoids. AEA and 2-AG enhanced the lipid synthesis of SZ95 sebocytes which was mimicked by synthetic CB_2 agonists and inhibited by CB_2 antagonists or siRNA mediated CB2 silencing. In good accordance with their lipogenic effect, ECs decreased the viability and induced apoptosis of the cells further supporting their role in promoting sebaceous differentiation. EC treatment resulted in a rapid Erk phosphorilation and later in increased expression of PPARs and target genes. Antagonists of both MAPK pathway and PPARγ inhibited the effect of the ECs. These data strongly argue for the involvement of the MAPK-PPAR pathway in the lipogenic effect of ECs.[78] Since both decreased and increased sebum production can play etiological role in several skin diseases, targeting of the sebaceous endocannabinoid system may have a notable therapeutic importance.[74]

Therapeutic properties: Phytocannabinoids and TRP ion channels

A possible way to utilize the ECS in the skin for therapeutic purpose is the modification of the EC tone by manipulating the activity of synthesizing or degrading enzymes.[74,85] Indeed, as Karsak et al.[81] convincingly demonstrated, the lack of epidermal cannabinoid signaling in CB1 and CB2 double KO mice resulted in aggravated allergic skin inflammation but the increased EC tone by genetic ablation of AEA metabolizing enzyme fatty acid amide hydrolase (FAAH) attenuated the inflammatory symptoms in a contact dermatitis rodent model. In a good agreement with the above findings, we also demonstrated that FAAH inhibitors (most probably via restoration of homeostatic anti-inflammatory EC tone) exert anti-inflammatory effects in human keratinocytes by inhibiting TLR2 induced pro-inflammatory signals.[86] Since sebocytes are significant source of cutaneous ECs,[78] their EC production can considerably contribute to the elevated EC tone upon FAAH inhibition, although direct effect

of FAAH inhibition has not been directly investigated in sebocytes yet.

Another promising approach to influence cutaneous ECS is targeting CB receptors with stable, exogenous ligands, like phytocannabinoids, the most well-known active ingredients of the cannabis plant.[85] Surprisingly, (−)-cannabidiol (CBD) a non-psychotropic phytocannabinoid, in contrast to ECs, decreased proliferation, inhibited lipid synthesis and evoked marked anti-inflammatory effects on SZ95 sebocytes.[87] The effect of CBD was found to be independent of CB_2 (mediating lipogenic effect of ECs) and mediated by other molecular targets. The anti-inflammatory effect of CBD were mediated by the activation of the A2A adenosine receptor resulting in up-regulation of tribbles homolog 3 (TRIB3) and consequent inhibition of the pro-inflammatory p65 NF-κB pathway in the downstream signaling. In contrast, the lipostatic and anti-proliferative effects of CBD was mediated by Ca^{2+} influx via TRPV4, a member of the transient receptor potential vanilloid (TRPV) cation channels. CBD was also reported as a week activator of TRPV4 in an earlier study.[88] On sebocytes, CBD inhibited cellular proliferation and suppressed lipid synthesis induced by arachidonic acid, linoleic acid and testosterone combination, or AEA. This general "sebostatic" (lipid decreasing and anti-proliferative) action of CBD was associated with the inhibition of ERK1/2 MAPK pathway and down-regulation of nuclear receptor interacting protein 1 (NRIP1, a.k.a. RIP140). Importantly, these effects of CBD were inhibited by pharmacological blockade of TRPV4 and mimicked by a synthetic TRPV4 agonist, strongly arguing for the sebostatic role of TRPV4[8585]. Similarly to TRPV4, activation of TRPV1[89] and TRPV3 (Szántó et al, unpublished manuscript) also suppressed lipid synthesis of sebocytes suggesting a lipid synthesis inhibiting effect for Ca^{2+}-coupled signaling pathways. This conclusion is also supported by the finding that removal of extracellular calcium and 1,25 dihydroxyvitamin D3 increased lipid synthesis of sebocytes.[90] Interestingly, we found that other phytocannabinoids can oppositely influence the lipid synthesis of sebocytes.[91] Like CBD, (−)-cannabichromene (CBC), (−)-cannabidivarin (CBDV) and (−)-Δ(9) –tetrahydrocannabivarin (THCV) significantly reduced arachidonic acid-induced lipid synthesis whereas (−)-cannabigerol (CBG) and (−)-cannabigerovarin (CBGV) increased basal sebaceous lipid production. Although their exact mechanism of action is not known yet, their different action on sebum production may be explained by their different affinity to CB receptors and/or TRP channels.[88,92,93]

It is tempting to translate the above experimental results into therapeutic exploitation. CBD possesses characteristic of an ideal anti-acne agent, alleviating several factors of this abundant inflammatory disease: (1) it exerts anti-inflammatory effect, (2) suppresses increased sebum production, as well as (3) pathologically accelerated cell proliferation in sebaceous glands. Activation of certain TRP channels and related Ca^{2+} signaling might also decrease sebum production whereas TRP channel antagonists or certain (phyto)cannabinoids activating CB_2 or increasing EC tone might be useful in treatment of dry skin associated diseases.[74,85]

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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