Steroids 103 (2015) 72–88

Contents lists available at ScienceDirect

Steroids

journal homepage: www.elsevier.com/locate/steroids

On the role of skin in the regulation of local and systemic steroidogenic activities

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ARTICLE INFO

Article history:
Received 26 January 2015
Received in revised form 21 April 2015
Accepted 21 April 2015
Available online 16 May 2015

Keywords:
Skin
Secosteroids
Homeostasis
Neuroendocrinology
UVR

ABSTRACT

The mammalian skin is a heterogeneous organ/tissue covering our body, showing regional variations and endowed with neuroendocrine activities. The latter is represented by its ability to produce and respond to neurotransmitters, neuropeptides, hormones and neurohormones, of which expression and phenotypic activities can be modified by ultraviolet radiation, chemical and physical factors, as well as by cytokines. The neuroendocrine contribution to the responses of skin to stress is served, in part, by local synthesis of all elements of the hypothalamo-pituitary–adrenal axis. Skin with subcutis can also be classified as a steroidogenic tissue because it expresses the enzyme, CYP11A1, which initiates steroid synthesis by converting cholesterol to pregnenolone, as in other steroidogenic tissues. Pregnenolone, or steroidal precursors from the circulation, are further transformed in the skin to corticosteroids or sex hormones. Furthermore, in the skin CYP11A1 acts on 7-dehydrocholesterol with production of 7-dehydropregnolone, which can be further metabolized to other Δ7steroids, which after exposure to UVB undergo photochemical transformation to vitamin D like compounds with a short side chain. Vitamin D and lumisterol, produced in the skin after exposure to UVB, are also metabolized by CYP11A1 to several hydroxyderivatives. Vitamin D hydroxyderivatives generated by action of CYP11A1 are biologically active and are subject to further hydroxylations by CYP27B1, CYP27A1 and CP24A. Establishment of which intermediates are produced in the epidermis *in vivo* and whether they circulate on the systemic level represent a future research challenge. In summary, skin is a neuroendocrine organ endowed with steroid/secosteroidogenic activities

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1. Skin as a sensory organ endowed with neuroendocrine activities

1.1. Structure and functions of the skin

The mammalian skin is a heterogeneous organ/tissue covering our body and showing significant regional variations in its structure and functions. Adult human skin has a surface area of approximately 2 m^2, is around 2.5 mm thick, and constitutes approximately 6% of our total body weight which exceeds all other organs except muscle, bone, adipose tissue and blood systems [1–3].

Skin is a multi layered organ composed predominantly of an external stratified, non-vascularized, epithelium (epidermis), underlying connective tissue (dermis), and the subcutaneous adipose tissue called the hypodermis [1–3]. The skin also produces several specialized miniorgans called appendages that include hair follicles, eccrine, sebaceous, apocrine glands, nails and mammary glands in the breast that penetrate deeply into the subcutaneous fat [1–6]. The human skin shows significant differences in histoarchitecture depending on anatomical location. In addition, there are significance differences in skin histology and physiology between humans and primates and furry animals including laboratory mice (Fig. 1) [2–6]. In the latter, terminal hair follicles cover most of the body serving as insulating cover and as touch organs, and the histology and physiological activities of their skin are dependent on the phase of the hair cycle [5–7].

Abbreviations: ABCA1, ATP binding cassette transporter A1; DHCR7, 3β-hydroxysterol Δ7-reductase; CRH, corticotropin releasing hormone; 7DHC, 7-dehydrocholesterol; 7DHP, 7-dehydropregnenolone; HPA, hypothalamic–pituitary–adrenal axis; GH, growth hormone; MC-R, melanocortin receptors; GR, glucocorticoid receptors; HSL, hormone sensitive-lipase; LXR, liver X receptor; MLN64, metastatic lymph node 64 protein; NCEH, neutral cholesteryl ester hydrolase; POMC, proopiomelanocortin; RARs, retinoic acid receptors; StAR, Steroidogenic Acute Regulatory Protein; SREBP-1c, steroid receptor element binding protein 1c; TRH, thyroid releasing hormone; TSH, thyroid stimulating hormone; UVR, ultraviolet radiation; VAD, vitamin A deficient; VDR, vitamin D receptor.

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http://dx.doi.org/10.1016/j.steroids.2015.04.006
0039-128X/Published by Elsevier Inc.

The epidermis stratifies and is a continually keratinizing or cornifying squamous epithelium that terminates at the muco-cutaneous junctions and consists of four major sub-layers composed predominantly of keratin-producing keratinocytes. The basal layer of the epidermis contains keratinocytes with stem cell-like properties and minor populations of Merkel cells (with sensory functions) and melanocytes (melanin-producing cells at a ratio of 1:36 with keratinocytes). Above it is the suprabasal layer followed by the stratum spinosum containing 8–10 sheets of keratinocytes with limited capacity for cell division among which are bone marrow-derived Langerhans cells (at a ratio of 1:53 with keratinocytes) [8]. Differentiating keratinocytes form the stratum granulosum (SG) composed of 3–5 sheets of non-dividing differentiating keratinocytes producing keratinohyalins that further differentiate to form the stratum corneum (SC). Lipids released from lamellar granules in the SG are probarrier lipids that are processed in extracellular spaces as the SC forms. These lipids includes glucosyl ceramides, cholesterol, cholesterol esters, other sterols and long-chain fatty acids, which are further metabolized or spontaneously organized into multiple layers between the corneocytes [9–12]. The SC represents a cornified layer of 15–30 sheets of non-viable, but biochemically-active cells called corneocytes linked by corneodesmosomes and surrounded by lipids, playing a critical role in the barrier function of the epidermis. This physical barrier not only protects against water loss or the harmful action or penetration of physicochemical elements from the environment into the skin and by association, the body, but also protects against microbial invasion by acidic pH (4.0–5.5) or by the presence of antimicrobial peptides and substances with antimicrobial and perhaps anti-viral activities [1,4,9]. The SC is also desquamating releasing metabolic by-products and sheading corneocytes each day that may have a microbial load or be harmful to local and systemic homeostasis elements. It must be noted that the pores of sweat glands and hair follicles disrupt this epidermal barrier providing potential entry points for environmental factors on one hand and serving as an exist points for secretory activity designed to protect local homeostasis on the other [4].

The epidermis is separated from the underlying dermis by the basement membrane which helps in defining the polarity of continuously renewing and differentiating squamous epithelium (see above) [1–3]. The dermis consists principally of fibroblasts/fibrocytes, a critical mesenchymal cell type which produces dense fibrous/elastic components as well as loose proteoglycans, glycoproteins, water and hyaluronic acid, and other amorphous and hydroscopic but biologically active molecules, altogether called the extracellular matrix (ECM) [1–3]. There are also other mesenchymal in nature cell types including fat cells and other surrounding structures such as vascular, neural and lymphatic systems and networks, excretory and secretary glands (sebaceous, eccrine and apocrine glands), and keratinizing structures including hair follicles and nails. Also, present are sensory nerve receptors of Meissner's corpuscles (touch), Pacinian corpuscles (pressure), Pilo-Ruffini corpuscles (mechanoreceptors), free nerve terminals which also penetrate the epidermis and hair follicles [1–4,6]. Additional elements of the dermis and hypodermis are represented by non-resident cell of hematopoietic origin contributing to the functions of the skin immune system. Both resident and circulating dermal cells, as opposed to epidermal and adnexal epithelial cells, are migratory cells communicating via their soluble secreted ECM components. In general, the dermis is divided into the papillary dermis adjacent to the basement membrane and the deeper reticular dermis adjoining subcutaneous adipose tissue/hypodermis. The latter is composed of fat-rich connective tissue connecting the dermis to the skeletal components and hosting the adnexal structures [13]. The thermoregulatory and mechanical functions of the dermis and hypodermis are appreciated. Fat lobules forming the hypodermis are separated by fibrous septae transverse rich in vasculature and play an important function in isolation, cushion and energy storage. Furthermore, the deep and superficial vascular beds deliver oxygen and nutritional and regulatory factors to the dermis/hypodermis (and by diffusion to the epidermis), Also, epidermal and dermal factors can enter the circulation for delivery to other body coordinating centers. These factors include vitamin D, cytokines, leptin, growth factors, neuropeptides, hormones and skin specific metabolites [4,13,14]. Furthermore, the extensive neural network collects information from all components of the skin to be processed by local, spinal cord, para- and sympathetic coordinating centers as well as by the brain, to coordinate the

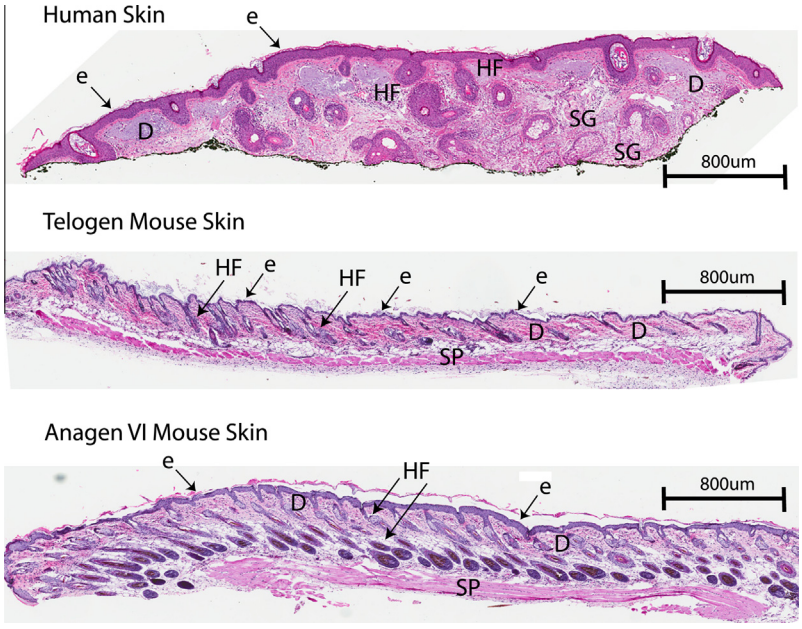

Fig. 1. Differences in the histostructure of the skin between human and mouse skin at telogen and anagen VI phases of the hair cycle. e: epidermis, D: dermis, HF: hair follicles: SG: sebaceous glands, SP: panniculus carnosus.