Neural control of skin water content: The sebaceous gland, a neglected target.

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Abstract

Normally supple and moist, the skin is the largest organ and outermost structure of the body. It is composed of separate but interconnected layers, working as a whole but controlled distinctively by numerous modulatory signals arising from several areas of the central, peripheral and autonomous nervous systems (CNS, PNS, ANS, respectively). Almost all functions mediated by that organ depend significantly upon water content levels of its constitutive layers. There is increasing evidence suggesting that a pivotal mechanism involved in water content modulation is the sebaceous gland. Its dysfunction has also been associated with debilitating dry skin problems such as xerosis, atopic dermatitis, psoriasis and rosacea. Generally, sebum secretion levels are considered to be dependent upon sex hormone (e.g. testosterone, DHEA) release – attributed to neuroendocrine actions (hypothalamus-pituitary-gonadal axis-control) on various organs. However, clear evidence indicate that specific neuropeptides and peripheral nerves can also participate significantly to the regulation of sebum secretion and, hence, to skin moisture and functions. This editorial aims at summarizing some of the main findings in neural control mechanisms of normal skin functions – specifically those associated with sebaceous gland activity.

Functional Anatomy of the Skin

The skin is the largest organ (~2 m²) of our body and the first line of defense from external factors. It prevents excessive water content losses and, as such, serves as a lipid-rich structure involved in regulating body temperature. The mammalian skin is composed of four layers – namely the epidermis, basement membrane, dermis and subcutaneous or hypodermis. None of the epidermis sublayers (stratum corneum or SC, granulosum or SG, spinosum, basal) contains blood vessels per se although the deepest layers are "nourished" so to speak by diffusion from blood capillaries extending to the upper layers of the dermis [1-3]. The dermis provides strength and elasticity to the skin through an extracellular matrix composed of collagen fibrils, microfibrils and elastic fibers, embedded in hyaluronan and proteoglycans [4]. It harbors blood vessels, mechanoreceptors, thermoreceptors and nociceptors that provide the sense of touch, pressure and heat as well as biological fluids released from sudoriferous and sebaceous glands [5,6].

Generally-Shared Knowledge about Neural Control of Skin Functions

The sensory roles attributed to skin functions are rather well-described in textbooks. Cutaneous nerves and sensory elements of the peripheral nervous system (PNS) respond to stimuli from the circulation and to emotions ("internal trigger factors") as well as from peripheral receptors (i.e., mechanoreceptors, nociceptors, thermoreceptors, chemoreceptors) by sending directly or indirectly to the CNS, inputs involved in sensations (hot/cold, pressure/touch, pain, vibration, chemicals, etc.), vasoconstriction, vasodilatation, body temperature regulation, barrier function, secretion, growth, differentiation, cell nutrition, nerve growth, inflammatory and immune responses, apoptosis, proliferation, and wound healing [1].

Water Content Levels and Skin Health

The inner milieu of our body consists of about 70% water (gender- and age-based differences ranging from 55-75%) whereas surrounding ambient air carries less than 1% water [2]. Consequently, skin water content tends to decrease more or less rapidly through sweating and evaporation and without normal mechanisms for steady replenishment of skin water content level, xerosis and other skin problems, for which skin dryness plays a role, are bound to be experienced. Two main mechanisms affect water content at the cellular level – 1) water transport from inner
layers towards the epidermis and, 2) water transport and evaporation from epidermal layers towards the exterior.

**Water Transport from Inner Layers to the Epidermis**

Skin hydration levels are regulated by water transport from inner layers, including from blood vessels, that seek bringing in water towards the dermis and, hence, to the epidermis. In other words, water travels from the deeper skin layers towards outmost skin layers to hydrate cells of the SC – where it is eventually being lost to evaporation. Increasing skin water content is thus achievable through enhanced activity of Aquaporin channels, supported by water-binding molecules such as glycerol, expressed on vascular endothelial cells where it facilitates water exchange and transport between blood and dermis [7]. In other words, body water levels as well as blood volumes, circulating flow levels and regional distribution can significantly affect skin water content levels [8]. Indirectly, neural control of water transport may be achieved by neuroendocrine responses (hypothalamic-pituitary-adrenal axis) through control of vasodilation and vasoconstriction. Arteriovenous anastomoses (AVAs) have been found to play a key role in cutaneous blood flow regulation – e.g. dilating AVAs for increased cutaneous vascular volume enabling more blood to enter deep skin layers [9]. More directly, other structures of the CNS can also alter vasodilation mechanisms - the medullary raphe nucleus, the rostral ventrolateral medulla oblongata, the preoptic area, the dorsomedial hypothalamus, the ventral tegmental area and the periaqueductal gray matter area [10-13].

**Water Transport and Evaporation from Epidermal Layers to the Exterior**

Although, water content levels vary accordingly to skin layer (70% in SG but 15-30% in SC), reducing water transport towards the outmost layers and increasing water-binding capabilities while reducing evaporation constitute another main mechanism of skin water content regulation [14]. Large reservoirs of water reside in the dermis where most water-binding molecules are expressed - the collagen fibers, the interstitial space glycosaminoglycans and the proteoglycans. A novel role of sebaceous glands in skin water content has recently been unraveled. The normal function of sebaceous glands is to produce and secrete sebum, a group of complex oils including triglycerides and fatty acid breakdown products, wax esters, squalene, cholesterol esters and cholesterol [15]. Sebum lubricates the skin to protect against friction and to make it more impervious to moisture. Furthermore, the sebaceous gland transports antioxidants in and on the skin and exhibits a natural light protective activity. It also possesses an innate antibacterial activity and has a pro- and anti-inflammatory function. It can regulate the activity of xenobiotics and is actively involved in the wound healing process. Neuropeptides constitute a heterogeneous group of biologically active peptides that are present in neurons of both the CNS and PNS. Thus, human skin and in particular the human sebaceous gland has been shown to express functional receptors for neuropeptides, such as corticotropin-releasing hormone, melanocortins, β-endorphin, vasoactive intestinal polypeptide, neuropeptide Y and calcitonin gene-related peptide [16]. Specifically, pathologically high levels of substance P and vasointestinal peptide expression have been shown to play a role in the pathogenesis of acne vulgaris. In response to stress, substance P can promote the development of cytoplasmic organelles in sebaceous cells, stimulate sebaceous germinative cells, and induce significant increases in the area of sebaceous glands. It also increases the size of individual sebaceous cells and the number of sebum vacuoles for each differentiated sebaceous cell, all of which suggests that substance P promotes both the proliferation and the differentiation of sebaceous glands [17]. The transient receptor potential vanilloid-1 (TRPV1) expressed in human skin, sebaceous glands in situ and in SZ95 sebocytes in vitro, when activated by capsaicin, its agonist, selectively inhibits basal and arachidonic acid-induced lipid synthesis in a dose-, time- and extracellular calcium-dependent and TRPV1-specific manner [18]. Most recently, using a novel line of transgenic mouse, it has been possible to demonstrate that Scd3-Cre-induced, diphtheria chain A toxin-mediated depletion of sebaceous lipids resulted in impaired water repulsion and thermoregulation [19].

**Conclusion**

All in all, these findings provide increasing evidence suggesting that key roles are played by neuropeptides and cutaneous nerves in sebaceous gland secretion and hence, indirectly, in skin water content through enhanced protective barrier and reduced water evaporation. These are promising mechanisms that may become new potential targets for the development of innovative CNS and/or PNS products against various types of dry skin problems. In the meantime and until such products get approval by authorities, recently identified, scientifically-based, topical creams may be used for temporary restoration of lipid-rich epidermal layers and stimulation of endogenous water transport mechanisms [20,21].

**References**

4. Breitkreutz D, Mirancea N, Nischt R. Basement membranes in skin: Unique matrix structures with


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