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Galanin family of peptides in skin function

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Abstract. The skin, the largest organ of the body, functions as a barrier between the body proper and the external environment, as it is constantly exposed to noxious stressors. During the last few years, the concept of an interactive network involving cutaneous nerves, the neuroendocrine axis, and the immune system has emerged. The neuroendocrine system of the skin is composed of locally produced neuroendocrine mediators that interact with specific receptors. Among these mediators are neuropeptides, including members of the galanin peptide family – galanin, galanin-message-associated peptide, galanin-like peptide, and alarin – which are produced in neuronal as well as nonneuronal cells in the skin. Here we review the expression of the galanin peptides and their receptors in the skin, and the known functions of galanin peptides in different compartments of the skin. We discuss these data in light of the role of the galanin peptide family in inflammation and cell proliferation. (Part of a Multi-author Review)

Keywords. Galanin, galanin receptor, inflammation, innate immunity, skin.

The galanin peptide family

The galanin peptide family consists of the 'parental' galanin; galanin-message-associated peptide (GMAP), which is derived from the same peptide precursor product as galanin; galanin-like peptide (GALP), encoded by a different gene; and the recently discovered peptide alarin, which is encoded by a splice variant of the *GALP* gene [1]. The galanin receptor family currently comprises three members, GALR1, GALR2, and GALR3, which are all G-protein-coupled receptors.

Nervous innervation and neurogenic inflammation

The innervated skin is a crucial barrier protecting the body from the environment. On the inside, the skin is directly connected to the central nervous system via cutaneous nerves (directly through afferent and efferent nerves, indirectly through the adrenal gland and the immune system). Two distinct groups of nerve fibers are found in the skin. The sensory nerves transfer signals from mechanoreceptors (like Meissner corpuscles and Merkel cells), thermoreceptors, or nocireceptors to the dorsal root ganglia via afferent, unmyelinated, slow (C) fibers or myelinated, fast (A) fibers. From there, sensations like pain, burning, and itching are forwarded to specific areas in the brain. The second group of nerves comprises sympathetic (cholinergic) and parasympathetic (also cholinergic) nerve fibers. These fibers mainly innervate anatomical structures in the dermis, including blood vessels, musculus erector pili, and eccrine glands. One other function of primary afferent neurons is the regulation of cutaneous blood flow, called antidromic vasodilatation. This reaction involves the release of vasoactive transmitters, including neuropeptide Y, calcitonin-gene-related peptide (CGRP), and vasoactive intestinal peptide from the peripheral varicosities of afferent

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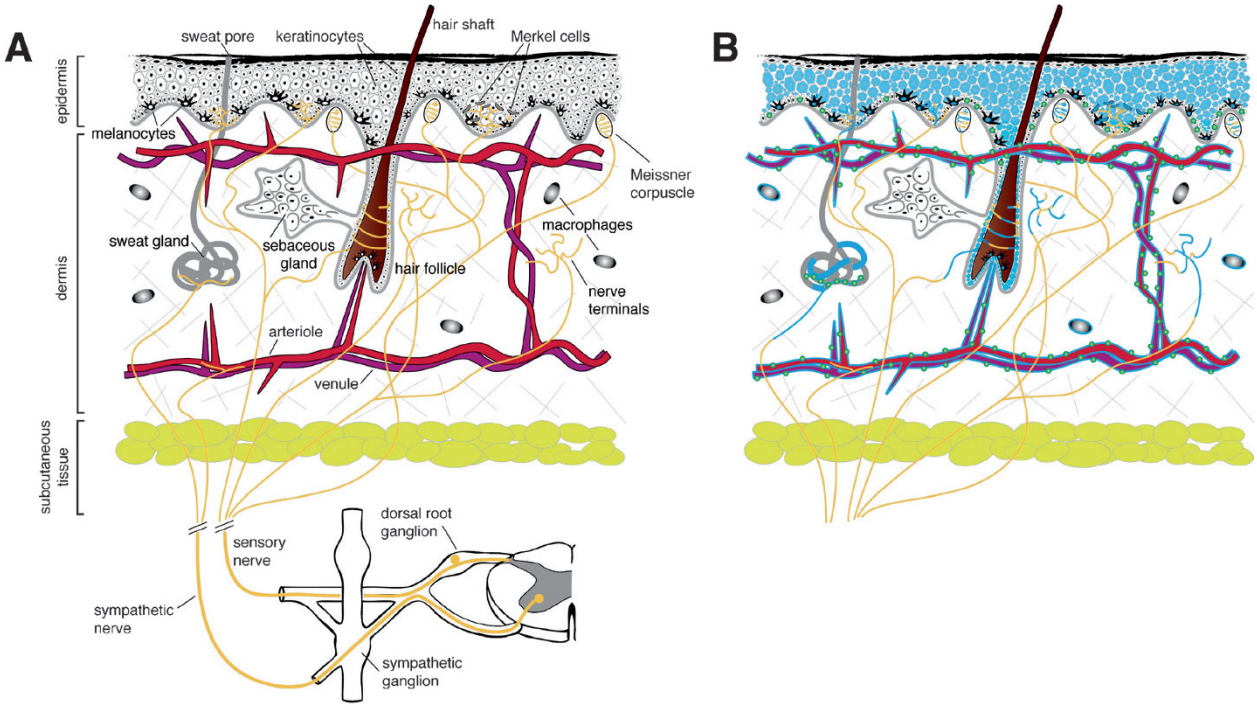

Figure 1. (*A*) Neuroanatomy of skin with regard to structures important to the galanin system. (*B*) Galanin and galanin binding sites in skin. Data are summarized from studies in human and rodent skin (taken from references mentioned in the main text). Blue staining indicates galanin expression (determined either by immunohistochemistry or *in situ* hybridization), and green dots indicate galanin binding sites as determined by receptor autoradiography.

neurons, leading to an increase in vascular permeability. These reactions to sensory nerve stimulation lead to leukocyte recruitment and are therefore commonly embodied in the term 'neurogenic inflammation' [2].

Galanin, which is also present in and released from the afferent nerves, counteracts the vasoactive actions via presynaptic and/or postsynaptic pathways. Besides its localization on afferent sensory neurons and specialized cutaneous sensory structures such as Merkel cells and Meissner corpuscles [3–8], galanin has been found in nonneuronal locations (Fig. 1, [9–11]). In human skin, galanin is also expressed in keratinocytes, eccrine sweat glands, and around blood vessels [12], suggesting functions other than those attributed to the nervous system (Fig. 1). It is notable that the highly abundant expression in the epidermis might be related to proliferative effects and immune functions, which are discussed below.

Galanin binding sites in human skin have been found in the vicinity of dermal arteries and arterioles and around sweat glands [12]. The divergent expression of galanin (highly prominent in the epidermis) and galanin binding sites (mainly in the dermis) suggests that the function of galanin that is transmitted via the galanin receptors is exerted mainly in the dermis (immune system and thermoregulation). GALP and alarin are expressed in keratinocytes at a low level [I. Rauch et al., personal communication]. In other tissues, GALP is able to signal through GALR2, but probably there is a genuine GALP receptor [13].

Alarin is expressed in perivascular locations, including pericytes and smooth muscle cells [14]. An alarin-specific receptor has not yet been identified.

Immune system and inflammation of the mammalian skin

Innate immunity is mediated by various humoral (e.g., alternative complement activation, antimicrobial peptides) and cellular defense mechanisms (e.g., macrophages) and is especially active in the early phase of skin defense against a pathogen. Innate immunity is nonspecific and does not change when the same pathogen is encountered again. The cells of the innate immune system recognize common characteristics of pathogens, or pathogen-associated molecular patterns (PAMPs), including lipopolysaccharides, peptidoglycans, and nonmethylated CpG islands in bacterial DNA. These PAMPs are recognized by various pattern recognition receptors, for example, Toll-like receptors, type II lectin receptors, C-type lectin receptors, Nod proteins, and integrins. The cell types belonging to the innate immune system include macrophages, mast cells, neutrophils, basophils, eosi-

nophilic granulocytes, natural killer cells, and dendritic cells. Pattern recognition receptors are also expressed by resident tissue cells such as keratinocytes, fibroblasts, and endothelial cells, which produce inducible nitric oxide synthase and antimicrobial peptides after stimulation.

Recent evidence suggests that GMAP – a proteolytic peptide derived from the galanin precursor protein – has antimicrobial activity, whereas galanin, GALP, and alarin do not [15]. Rauch et al. described suppression of growth and the budded-to-hyphal-form transition of *Candida albicans* for GMAP [15], indicating that GMAP is effective against *C. albicans* dimorphism and may thus reduce fungal progression and the spread of infection in host tissues.

The acquired immune system is mediated by antigen-specific humoral effectors (e.g., antibodies) and cellular components (e.g., lymphocytes) and governs immunological memory. It is activated, for example, when the innate immune system is not able to defend the body against a new infection. Antigen-presenting cells present antigens to recirculating lymphocytes in peripheral lymphoid tissue. The lymphocytes respond by proliferating and differentiating into effector cells, which can eliminate infection. In normal skin, these lymphocytes are T cells present around postcapillary venules, with about the same proportion of CD4-positive and CD8-positive cells with a 'memory' phenotype (CD45 RO+).

Because the postcapillary venules are where lymphocytes transmigrate through endothelial vessels to initiate inflammatory reactions, it is of interest that several research groups have shown that members of the galanin peptide family regulate the physiology of skin vessels, for example, vascular diameter and permeability in different species. In these studies, galanin inhibited cutaneous plasma extravasation induced by histamine [16–19] or antidromic C-fiber stimulation and substance P (SP) [20], results which have been confirmed in the microvasculature of the hamster cheek pouch [21]. Vasoconstrictive effects were also seen for galanin, GALP, and alarin upon coinjection of SP and CGRP into murine dorsal skin [14, 22].

Transgenic mouse models further substantiate the antiinflammatory function of galanin peptides in the skin. Galanin-overexpressing mice displayed a significant reduction in cutaneous plasma extravasation upon activation of neurogenic inflammation induced by mustard oil [23]. Unexpectedly, adult mice carrying a loss-of-function mutation in the galanin gene (galanin-knockout) lack an acute inflammatory edema response induced by coinjection of SP and CGRP. In addition, galanin-knockout animals also exhibit a deficit in neutrophil accumulation in the skin after exposure to noxious heat, carrageenin, or tumor necrosis factor alpha [24]. It is unclear whether this is due to a specific lack of galanin in the adult mouse or whether an associated developmental sensory neuronal deficit [25] contributes to the observed phenotype. If the latter, it would suggest that the sensory nerves that are galanin-dependent during development play a crucial role in the adult animal in the acute inflammatory response in the skin.

All these reports describe an indirect regulatory role for galanin peptide in cutaneous host defense. The only report so far indicating that galanin is expressed in immune cells of the cutaneous system is that of Ji et al. from their research in rats [26]. The authors found galanin to be expressed on 'immune cells' in the dermis of their inflammatory model. The marker antibody was ED-1, suggesting that these cells are macrophages. This is further supported by RT-PCR analysis in our laboratory, indicating substantial expression of galanin mRNA in macrophages [I. Rauch and R. Lang, personal communication].

The expression and distribution of galanin receptors in the skin is currently a matter of discussion. In contrast to the clear data showing galanin receptors located in the dermis around blood vessels, their presence on keratinocytes is less certain. I^{125}-galanin-ligand-binding assays on human skin biopsies and cultured keratinocytes revealed no galanin binding and only sparse galanin binding sites in the basal layer of the epidermis (Fig. 1, [12, 26]). Galanin receptor expression is activation-dependent in other epithelial systems, since stimulation of colonic epithelial cells by pathogens induces GALR1 expression [27, 28]. In contrast, several studies report galanin receptor mRNA expression in both cultured primary and transformed keratinocytes [29, 30]. The reason for this discrepancy stems partially from the fact that cultured human primary keratinocytes are an artificial system in which many artifacts occur through proliferation activation by several added growth factors in the culture medium. The physiological significance of GALR2 found on cultured keratinocytes, and probably mediating production of interleukin 1 and interleukin 8, needs to be supported by *in situ* hybridization and pharmacological studies [29, 31]. Especially striking in these studies was the abundant expression of GALR2 in immunohistochemical staining of normal human epidermis [29]. In apparent contrast to this finding, almost no GALR2 was found by Western blotting of tissue extracts compared to the level found in brain tissue. Another reason for the discrepancies is differences in galanin receptor distribution at various anatomical sites, an idea supported by findings that cultured keratinocytes derived from a human breast skin

specimen express only *GALR2* mRNA and protein [29], whereas human immortalized oral keratinocytes express mRNA and protein of all three galanin receptors [30].
It is likely that there is a common physiological background for these apparent discrepancies. Immediate effects of galanin peptide administration such as vasoconstriction might require a high density of receptors, which is present in the dermis. For long-lasting effects on transcriptional regulation and cell proliferation, a much lower level of expression of galanin receptors, not detectable by classic binding experiments, might be sufficient.

Proliferation and wound healing

Wound healing is a highly dynamic process and involves complex interactions of extracellular matrix molecules, soluble mediators, various resident cells, and infiltrating leukocyte subtypes. In the process of regaining tissue integrity, three phases – inflammation, tissue formation, and remodeling – are discriminated [32]. Thus, after injury, an inflammatory response governed by infiltrating leukocytes precedes the proliferation of endothelial cells, macrophages, keratinocytes, and fibroblasts. Exact regulation of these processes is necessary because, otherwise, physiological proliferation turns into malignant proliferation, ultimately leading to cancer growth. Remarkably, many neuropeptides have proliferative activity in the skin. Pivotal in this respect is SP, acting on neurokinin A receptors, which induces proliferation in keratinocytes and fibroblasts. Whereas there is some evidence for galanin as a mitogenic factor in tumors [30, 33–35], the bulk of current knowledge suggests that galanin has antiproliferative activities in normal and malignant tissue [36–39].
Recently, the differential expression of galanin receptors on tumors derived from epithelial cells was analyzed thoroughly. Expression of GALR1 in oral squamous carcinoma seems to convey antiproliferative effects [30, 40]. Henson et al. showed that addition of an inhibitory antibody directed to the ligand-binding domain of GALR1 induced proliferation in immortalized and malignant keratinocytes. These *in vitro* studies are complemented by the finding that chromosomal region 18q, harboring the *GALR1* gene, frequently carries aberrations in oral cancers. In the latter report, overexpression of GALR1, together with treatment with galanin, suppressed proliferation *in vitro* and *in vivo* in a human oral squamous carcinoma cell line via ERK1/2 activation.
In tumors of melanocytes immunohistochemical analysis of galanin expression revealed that galanin staining is higher in melanomas than in melanocytic nevi [41]. In nontransformed primary melanocytes galanin expression has been shown to be upregulated by Q-switched Ruby laser, which is used in the clinical setting for the treatment of pigmented lesions [42]. Interestingly, the human GALR1 receptor was cloned from the human melanoma cell line (HBMC, [43]), but to our knowledge no data regarding galanin receptor expression in melanomas are available.

Future perspectives

That there is extensive splicing in the *GALP* gene raises the possibility that new members of this peptide family remain to be discovered [14]. Furthermore, recent evidence suggests that GALP acts through a distinct receptor [13], leaving the receptors for GALP and alarin still to be found.
A wide area of research has been opened by the recent discoveries of the diverse actions of galanin peptide family members in epithelial biology. Moreover, it may become possible to derive diagnostic benefit from this new knowledge. Recently, galanin was found to be upregulated in colon carcinoma, prompting speculation that it might be fulfilling a role in immune surveillance of malignant tissue and highlighting its potential as a novel biomarker for certain types of cancer [44].
Peptides of the galanin family also are being considered in the therapeutic arena. Galanin receptors are G-protein-coupled receptors (GPCRs), which are excellent drug targets and usually inhibited by small molecules. A number of galanin antagonists [1] have already been defined in the search for novel pain medications. To activate the antiinflammatory capability of galanin peptides, selective agonists would be necessary. For treatment of inflammatory skin diseases like psoriasis, atopic dermatitis, and urticaria, topical application would be sufficient, avoiding possible systemic effects of the galanin-peptide agonist in the circulation.

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