Neurotrophins in healthy and diseased skin

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Neurotrophins (NT) exert their functions through two transmembrane receptors, the low-affinity receptor p75NTR and the high-affinity receptors trkA, trkB and trkC. Autocrine NGF stimulates keratinocyte proliferation through its high-affinity receptor trkA, while K252, a specific inhibitor of trk phosphorylation, blocks this effect. In addition, K252 and anti-NGF antibodies, induce apoptosis in human keratinocytes, indicating that autocrine NGF protects these cells from p53- and -75NTR-mediated cell death through its high-affinity receptor. While NGF, released from keratinocytes, exert neurotropic properties and stimulate dermal fibroblasts and melanocytes, these cells produce NGF that in turn release only NT-4. Melanocytes treated with TPA express trkA and trkB, but not trkC. NT-3 stimulates melanocyte proliferation, whereas they stimulate the synthesis of tyrosinase. NT-4, which is the only NT released by melanocytes acts in an autocrine manner for melanogenesis. Both dermal fibroblasts (DF) and myofibroblasts (MF) synthesize and release all NTs. In addition, DF and MF express all NT receptors except for trkC. NGE, BDNF, NT3 or NT4 promote fibroblasts differentiation into myofibroblasts, as they induce α-smooth muscle expression with an effect similar to the one produced by TGF-β. Moreover, NGF and BDNF, but not NT3, and NT4 stimulate isometric contractile strengths in living dermal equivalents, as measured by the Glasbox device. Furthermore, scratching assay performed on fibroblasts treated with all four NTs, demonstrates that NGF, BDNF or NT3 also induce fibroblasts migration. These data clearly indicate that the NT network in the skin could be responsible for a variety of functions, from interference with UV damage to melanogenesis, from regulation of contractile properties of the dermis to control of epidermal homeostasis.

Skin mast cells and cutaneous sensory nerves – duo infernale of pruritus

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Mast cells (MCs) are key contributors to many chronic inflammatory and pruritic skin conditions such as urticaria and atopic dermatitis. MCs release such mediators as proinflammatory cytokines, growth factors, histamine, and proteases, which are beneficial to the host in the acute phase of an allergic reaction but may contribute to skin inflammation and chronic disease. MCs are present, for example, in skin lesions of allergic contact dermatitis, psoriasis, and atopic dermatitis.

Neuroreceptors involved in prurition

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Itch was regarded for a long time as subspeciality of pain. Now it had become clear that prurition is mediated by specialized peripheral and central neurons. However, nociception and prurition show overlapping immunoneurological mechanisms and central perception areas. Umeated skin C-fibers of different classes are involved in induction of several itch qualities. Mechano-insensitive C-fibers express the histamine receptor and mediate almost pure itch. Histamine is involved for example in urticaria-induced itching and may be suppressed with antihistamines. Only recently, mechano-responsive polymodal C-fibers were identified to mediate next to pain also itch. These intraepidermal C-fibers were further identified to express several receptors involved in prurition. For example, the transient receptor potential vanilloid 1 (TRPV1) may induce burning pain and aggravate pruritus. Thus, targeting the receptor by its ligand capsaicin may serve as therapeutic intervention in chronic pain and pruritus. Also endothelin receptors and the proteinase activated receptor 2 (PAR-2) are expressed on the mechano-responsive polymodal C-fibers and mediate itch. Current investigations disclosed that many of the involved neuroreceptors are co-expressed, interact and potentate their effects. As a consequence, chronicization of itch-sensing is facilitated. Therefore, inflammatory cells such as neutrophils and monocytes are key contributors but under the influence of the diverse itch quality.

"JMRI brain scan studies in dermatology"

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Functional magnetic resonance imaging (fMRI) of the brain is able to anatomically...
map areas responsible for a variety of cerebral functions. The technique is dependent on blood oxygen levels. We have used fMRI to investigate whether the social impact of psoriasis is associated with altered cognitive processing of the expression of disgust. We demonstrated that psoriasis patients have significantly smaller signal responses to disgust as compared to neutral facial expression in the bilateral insulae as compared with healthy controls. There was no difference between the groups in terms of processing of fearful facial expressions. This would indicate that patients develop a coping mechanism by blocking processing of disgusted facial expressions encountered in others. We have also investigated the cerebral processing of itch using a placebo-controlled (MRI) experimental design and a novel time-series analysis technique using either histamine or saline injected into the volar left forearm. During the histamine scan, all volunteers perceived itch and developed a wheal and flare reaction. In contrast in the saline control there was minimal itch, and wheal and flare reactions were not observed. We showed that there was involvement of the bilateral pre-frontal motor cortex superior and mid-temporal gyri, cerebellum, anterior insula and postcentral gyri in itch processing. These studies, taken together, provide further evidence for the presence of a “brain-skin axis”.

Psychoneuroimmunology – clinical implications
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Progress in basic science resulted in the discovery of many mechanisms related to neuropeptides in the skin. These substances are released from peripheral cutaneous nerves during the physiological response to various nociceptive stimuli as well as in disease states. Both histamine from mast (MC) cells and endothelin 1 from endothelial cells and mast cells may induce neurogenic inflammation through their specific receptors on cutaneous sensory fibres H1 and ETA respectively. Neurogenic inflammation is altered in both psoriasis and atopic dermatitis (AD). The activation of vanilloid receptor VR1 is related to pruritus/burning and erythema induced during external calcineurin inhibitor treatment in numerous dermatological diseases. Keratinocytes (KC) are the source of nerve growth factor (NGF), that is neurotropin responsible for cutaneous nociception, nerve development and reconstruction of peptidergic C fibres after injury. Other receptors i.e. thermoreceptor on sensory C and filters Aδ fibres, namely VR1 (transient receptor potential, TRPV1) and cold receptors (TRPM8) on myelinated Aδ fibres might be responsible for itching and burning sensation. Endogenous opioid system is involved in antinociceptive pruritogenic effect in the skin after opioid binding to receptor: β-endorphin-MOR (μ), enkephalins – KOR (δ), and dynorphins – KOR (κ). β-endorphin upregulates some functions of keratinocytes – TGFβR2 expression, cytoketerin 16 production and migration of KC. It stimulates proliferation of melanocytes and plays a role in psoriasis, BCC and wound healing. Chronic itch was related rather to MOR, whereas acute itching to the activity of KOR agonists similarly to histamine, prostaglandins, leukotrienes, SP and CGRP, tryptase etc. Important pruritogenic factor in the pathogenesis of AD are proteinase activation receptors (PAR2) on skin nerves, which are stimulated by tryptase from MC or by other neutral proteinases. New strategy to suppress nociception is N-palmitoylethanolamine (PEA) which bind cannabinoid receptors CB1 and CB2 which is followed by release of opioids to the skin. These complicated network of neuropeptides is modulating both KC function and immunological response in the skin.

ItchyQoL and CU-Qol – novel instruments for measuring quality of life in patients with pruritic skin disorders
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Pruritus is a widely spread symptom in numerous dermatologic and systemic diseases that may have an enormous impact on patients’ daily life. The high individual burden of chronic pruritus along with the difficulty in objectively measuring pruritus intensity makes the assessment of quality of life (QoL) a suitable instrument to evaluate the impact of itch and the efficacy of its therapy upon a patient. Chronic spontaneous urticaria (CU) is a common skin disorder which is characterized by intense pruritus and spontaneously arising wheals and/or angioedema, occurring on a regular basis for longer than 6 weeks. Patients often suffer from CU for many years, and it has repeatedly been found that CU has a substantial impact on patient quality-of-life. In general, a better understanding of QoL in pruritus and CU patients is necessary for both clinical research and routine patient care. In clinical research, QoL measurements provide a rich evaluation of the benefits of a treatment, as experienced from the patient’s perspective. In routine care, QoL measures can provide physicians with a better understanding of the ways in which they can help their patients. Although there are many excellent general and dermatological QoL questionnaires, there were until recently no questionnaires available specifically designed for pruritus or CU patients which address the aspects of QoL most relevant to their condition. In the last years, ItchyQoL, an instrument for assessing the pruritus-specific QoL, and CU-Qol, a tool to evaluate the impact of CU on QoL, have been developed in English and Italian, respectively, and proven to be reliable, valid and responsive. We have translated both original instruments into German, culturally adapted, retranslated and tested them in cooperation with the original authors. Further translations of these questionnaires into various different languages are now of importance as these tools can then be used for the conduction of international studies with pooled data which would allow, for example, for an objective evaluation of the impact of certain treatments on the QoL in large numbers of pruritus or CU patients from different nationalities. Future use of these patient-related outcome measures may improve efficacy of treatment in pruritus and CU patients and generate direct patient benefit.

www.jidonline.org S105