A reliability assessment of standardized human surrogate models of histaminergic and non-histaminergic itch using histamine and cowhage spicules

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We previously reported that decreased level of semaphorin 3A (Sema3A) induces epidermal hyperinnervation in AD. To defend against pathogens, skin contains antimicrobial peptides that are induced by inflammation. Reduced induction of antimicrobial peptides, including cathelicidin LL-37 and human β-defensins (hBDs), in lesional skin of AD patients was suggested to increase susceptibility to infections. Here, we investigated the effects of antimicrobial peptides, including LL-37 and hBD-1-4, on Sema3A expression in normal human epidermal keratinocytes (NHEKs). We found that treatment with LL-37, but not hBDs, enhanced Sema3A expression. This LL-37-induced Sema3A expression was completely inhibited by pertussis toxin, an inhibitor of Gi subfamily of G protein α and by PD98059, an inhibitor of ERK1/2 signaling. Moreover, analysis of LL-37 receptors showed that P2X7R may be at least partly involved in LL-37-induced Sema3A expression in NHEKs. Thus, in addition to antimicrobial activity, cathelicidin LL-37 may contribute to the induction of Sema3A expression in NHEKs via certain Gi-coupled receptors and the ERK1/2 signaling pathway.

PP15

OVEREXPRESSION OF HISTIDINE DECARBOXYLASE IN THE EPIDERMIS OF PRIMATES WITH CHRONIC ITCH

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Recently, an increase in epidermal histidine decarboxylase (HDC), a key enzyme for histamine synthesis, has been shown to be involved in acute and chronic itch-related behaviors induced by topical application of anionic surfactants in mice. Moreover, HDC was up-regulated in the epidermis of atopic dermatitis patients. These findings suggest the possibility that increased HDC in the epidermis plays a role in skin conditions with chronic itch. The aim of this study was to investigate whether the expression of epidermal HDC is increased in primates with idiopathic chronic itch. The skin biopsies were collected form 8 adult female Cynomolgus macaques (Macaca fascicularis) with varying degrees of idiopathic chronic itch. The expression of HDC was quantified by immunohistochemistry and analyzed in a blind manner. A significant positive correlation was observed between expression level of epidermal HDC and time spent in spontaneous scratching (Pearson Correlation, r=0.734, p=0.038). The expression was limited to the upper epidermal layers. The up-regulation of HDC in the upper epidermis may be involved in skin conditions with chronic itch.

CLINICAL RESEARCH TRACK – METHODOLOGY FOR ITCH

PP16

A RELIABILITY ASSESSMENT OF STANDARDIZED HUMAN SURROGATE MODELS OF HISTAMINERGIC AND NON-HISTAMINERGIC ITCH USING HISTAMINE AND COWHAGE SPICULES

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Recent discoveries in itch neurophysiology have led to an increased use of human surrogate models of both histaminergic and particularly non-histaminergic itch. However, no absolute or relative reliability assessments have been conducted for these models and methods for induction of itch using cowhage are highly variable. This study sought to standardize cowhage application and to perform a test–retest reliability-assessment for the application of both histamine and cowhage. 3 doses of cowhage (5, 15 and 25 spicules), and 1 dose of 1% histamine were applied in 4 areas on the volar forearm in 15 healthy male volunteers. All measurements were performed twice, 7.73 days (±0.73 SEM) apart. Itch- and pain-intensity were rated on a co-VAS. Spatial itch distribution, TEWL and blood perfusion were monitored. Measures of reliability were coefficient of variation (CV) and intra-class correlation (ICC) for each itch provocation. Stimulus-response-associated differences were found between doses for the intensity of itch and the peak itch intensity (p<0.05). The reliability assessment for the itch intensity exhibited good intra-individual reliability (ICC = 0.57–0.83) and modest absolute reliability (CV = 25.4–156.6) for both cowhage and histamine-induced itch. Quantification of the spatial perception of itch exhibited low reliability.

CLINICAL RESEARCH TRACK – PRURIGO AND OTHER PRURITIC SKIN

PP17

CORRELATION OF PLASMA GRANZYME B LEVELS WITH PRURITUS OF ATOPIC DERMATITIS

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Clinically, atopic dermatitis (AD) associated pruritus is resistant to conventional treatment, including histamine H1 receptor antagonists. Granzymes (Gzms), a family of serine proteases expressed by cytotoxic T lymphocytes and natural killer cells, have been shown to modulate inflammation. Their relationship with pruritus of AD still remains unclear. In the present study, we assessed relationships among plasma Gzm levels and severity of pruritus or dermatitis in AD patients. In enzyme-linked immunosorbent assays, plasma GzmB levels were significantly increased in AD patients. Correlation analyses among other clinical markers of AD showed that plasma GzmB levels positively correlated with plasma gastrin releasing peptide (GRP) level, serum thymus and activation-regulated chemokine (TARC) levels or scoring atopic dermatitis (SCORAD). Visual analogue scale (VAS) score also tended to correlate with plasma GzmB level. On the other hand, plasma GzmA levels showed no correlation with these clinical markers. These data suggest that plasma GzmB levels may be involved in the severity levels of both pruritus and dermatitis in AD patients.