ABSTRACTS

NEUROBIOLOGY OF THE SKIN SESSION

ESDR MEETING BARCELONA

Thursday 8 September 2011, 8.00-10.30

Abstracts

The p75 neurotrophin receptor modulates differentiation and apoptosis in transit amplifying keratinocytes
Carlo Pincelli, University of Modena and Reggio Emilia, Italy
p75 neurotrophin receptor p75NTR, belongs to the TNF-receptor superfamily and signals apoptosis.
We evaluated the expression and function of p75NTR in human keratinocytes. p75NTR was found to be involved in keratinocyte keratinocyte. p75NTR in the skin. Moreover, calcium treatment of subconfluent keratinocytes induced the up-regulation of p75NTR concurrently with the expression of the differentiation markers. p75NTR retroviral infection of stem cells induced a more differentiated phenotype with the same features of TA cells. On the other hand, when p75NTR was silenced, calcium treatment failed to induced differentiation in subconfluent keratinocytes. Moreover, b-myeloid, a ligand for p75NTR, induced apoptosis in human keratinocytes only in p75NTR expressing keratinocytes, as shown by caspase-3 activation. Brain-derived neurotrophic factor (BDNF) or neurotrophin-4 (NT-4), which signal through p75NTR, determined a higher rate of apoptosis in HaCaT cells overexpressing p75NTR. On the other hand, NT-4 failed to induce cell death in p75NTR-knockout HaCaT cells. Because p75NTR is characterized by a dysregulation of epithelial homeostasis, namely alteration of differentiation and resistance to apoptosis, we evaluated the expression and function of p75NTR in this disease. p75NTR was absent in lesional psoriatic skin and p75NTR levels were significantly lower in psoriatic than in normal TA keratinocytes. The rate of apoptosis in psoriatic TA cells was significantly lower, as compared to normal TA cells. p75NTR retroviral infection restored apoptosis in psoriatic keratinocytes. These results suggest that p75NTR has a dual role: it acts as a "switch on" cell differentiation and/or as a pro-apoptotic receptor. Thus, p75NTR is essential for maintaining epithelial homeostasis.

Effect of chronic mild stress on skin and brain in the NC/Nga atopic-like mouse
Klas Nordlind, 1 S-B Linne-Rahm, 1 H Eilbert, 1 A Rasul, 1 L Grips, 1 M Holst, 1 B Johansson, 1 L Ohlson, 1 E Theodoreson 2 and RD Blakely 1 1 Department of Medicine, Solna, Dermatology and Venereology Unit, Karolinska Institutet, Stockholm Sweden, 2 Department of Woman and Child Health, Astrid Lindgren Children's Hospital, Solna, Stockholm, Sweden, 3 Departments of Molecular Medicine and Surgery, and 4 Neuroscience, Karolinska Institutet, Stockholm, Sweden, 5 IJK/Chemical Biology, University Hospital, Linköping, Sweden and 6 Department of Pharmacology and Center for Molecular Neuroscience, Vanderbilt University Medical Center, Nashville, TN, USA
Atopic eczema is often worsened by stress. We have studied the effect of chronic mild stress in the atopic-like NC/Nga mouse strain. The mice were subjected to chronic mild stress for 12 weeks and eczema was induced by applying a mitogen (Dermatophagoides pteronyssinus) on the ears for the last 4 weeks. The mice were divided into stressed eczematous, non-stressed eczematous and stressed control groups. Serum corticosterone levels were determined at the endpoint of the experiment. The biopsies from skin and brain have been analyzed using immunohistochemistry and RT-PCR. The diameter of the ears was larger in the stressed eczematous group compared to the other groups. Moreover, the corticosterone levels were significantly lower in the stressed eczematous group. The neuremediators being studied are serotonin, its transporter protein, as well as its receptors, and the tachykinin substance P and its receptor neurtikin-1.

Regulatory mechanisms of epidermal innervations in atopic dermatitis
Kenji Katamori (Chiba, Japan) Department of Dermatometry, Juntendo University Urayasu Hospital, Chiba, Japan
Histamine, the best known pruritogen in human is also regarded as an experimental itch-causing substance. Clinically, antihistamines, i.e., H1-receptor antagonist, are commonly used to treat all types of itch. However, antihistamines often lack efficacy in patients with chronic itches where other agonists may be involved including proteases, neuropeptides, cytokines, and opioids, and their cognate receptors, such as thermoreceptors, PAR-2, and opioid receptors. Such pruritogenic mediators and mediators released in the periphery may directly activate itch-sensitive C-fibers by binding to specific receptors on the nerve terminals. Nerve fibers can also be activated by exogenous mechanical, chemical, or biological stimuli, resulting in itch responses. Histological examination reveals that epidermal nerve densities are increased in patients with AD, suggesting that the higher density is partly responsible for the intense itching in the skin. Such hyperinnervation is probably caused by an imbalance of nerve elongation factor(s), nerve growth factor, amphiregulin, gelatinase) and nerve repulsion factors(s, e.g., semaphorins 3A, 3A and nerve growth factor receptor antagonist(s, e.g., TRK-A receptors. We recently demonstrated that neuronal matrix metalloproteinase-2 is involved in penetration of sensory nerve fibers into basement membrane through modulation by axonal guidance molecules. Clinically, VPUVA therapy reduces epidermal hyperinnervation in patients with AD by normalization of SemA3A and NGF expression in the epidermis, leading to decrease in scores on pruritus. Such anti-nerve growth effects were found in the dry skin of acetone-treated mice treated with narrowband UVB. Today I would like to talk about the penetration mechanisms of nerve fibers into the epidermis in AD.

Pruritus – from bench to bedside and back
Martin Metz and Marcus Maurer Dept. of Dermatology and Allergy, Allergie-Centrum-Charité, Charité – Universitätsmedizin Berlin, Germany
Pruritus is a major symptom of numerous skin and systemic diseases and causes a substantial burden on patients’ quality of life. The pathophysiology of itch is very diverse and it involves a complex network of cutaneous and neuronal cells which may vary substantially depending on the underlying disease. Experimental pruritic diseases have enabled us in recent years to identify some new mediators and receptors which might be critically involved in chronic pruritus in some patients. Some of these findings have led to the development of novel pharmacological approaches aimed at the treatment of chronic pruritus. On the other hand, findings in patients and healthy subjects have led to hypotheses of specific itch-inducing mechanisms which have then been verified and characterized to some extent in experimental models. We and others have contributed to improve diagnosis and treatment of patients with chronic pruritus and to better understand the pathophysiological mechanisms underlying chronic pruritus. Here we will present the current thinking in the field, recent advances in basic science and clinical research, as well as novel approaches for the diagnosis and treatment of pruritus.

New Insights into the Brain-Skin Axis
Elyse Kley and Christopher CM. Griffiths Dermatological Sciences, University of Manchester, Manchester, UK
Our recent studies on the pruritogenic mediator histamine suggest that the brain may play a role in the regulation of pruritus. Histamine-induced itch is mediated by the histamine H1-receptor, and H1-receptor antagonists have been shown to reduce pruritus in patients with chronic pruritus. The aim of this study was to investigate the role of H1-receptors in the regulation of pruritus in patients with chronic pruritus and in healthy volunteers. Using functional magnetic resonance imaging (fMRI) study of the cerebral processing of histamine-induced itch in healthy volunteers (n=16) by tracking the 8 minute period following a single skin prick. Histamine-induced itch resulted in a significant positive signal in pre-hypothesised regions including the prefrontal motor cortex (Brodman Area (BA) 6), mid-frontal gyrus (BA 10), postcentral gyrus (BA 3/4), somatosensory cortex (BA 41), inferior parietal cortex (BA 40) and posterior insula. A time-series analysis demonstrated progressive activation of distinct regions of the prefrontal and parietal cortex with time following histamine. The results suggest that the brain may play a role in the regulation of pruritus. Histamine-induced itch is mediated by the histamine H1-receptor, and H1-receptor antagonists have been shown to reduce pruritus in patients with chronic pruritus.

HNP-1 axis activity and stress reactivity in psoriasis
Anita WEM, Evens Radboud University Medical Centre Nijmegen, The Netherlands
As the stress response involves activation of the HPA axis, which interacts with the immune system, stress-related factors might influence immune-mediated diseases, such as psoriasis, for example by affecting the secretion of proinflammatory cytokines. In this presentation, we give an short overview of several experimental and prospective studies about the possible relationship between psychophysiological stressfactors and the disease course of psoriasis. Preliminary evidence was found for a relationship between stressfactors and the course of psoriasis, for example by an altered cortisol response during exposure to stress. Increasing evidence further suggests that these factors seems to be particularly relevant during phases of high levels of daily stressors and for patients who report heightened stress levels during a longer period of time. Possible psychopharmacological pathways and innovative tailorred therapy options of psychopharmacological treatment combinations will be discussed.

Evaluation of a psychological group intervention for patients with moderate and severe psoriasis
Lucia Tomas-Aragonés and Servando E. Maren Dermatology, Department Alcaliz Hospital, Tarragona and Psychology Department, University of Zaragoza, Aragon Health Sciences Institute (I+CS), Spain
Psoriasis is a chronic disease in which psychological distress is a common part of the illness experience. The burden of coping with a chronic disease can have a negative impact on the patient's quality of life and psoriasis patients frequently report poor self-esteem and high levels of psychological stress. Psychoeducational groups focus on educating patients about their disorder and ways of coping. Current, up-to-date information is provided by the health professional and the participants share their concerns and strategies used to overcome difficulties related to their illness. A pilot study using a randomized control trial was conducted. A total of 30 patients with moderate to severe psoriasis were randomly assigned to the control or intervention group. The 10 patients in the intervention group were offered 12 weekly sessions of 90 minutes psychoeducational group therapy, consisting of health education, enhancement of problem-solving skills, stress management, and psychological support. The patients were assessed at baseline, before random assignment, and at the end of the 12 weeks. Inclusion criteria: Psoriasis Area Severity Index (PASI): ≥ 5.Dermatology Life Quality Index (DLQI) ≥ 6; Hospital Anxiety and Depression Scale (HADS) ≥ 11 in either the depression or the anxiety scale; signed consent form and willingness to participate. The preliminary results of the first intervention group and control group will be presented and discussed, as well as explaining the programme and the development of the group sessions. Finally, we will give an overview of the state of knowledge in psychoeducational group interventions for psoriasis patients and highlight the need to create evidence of its effectiveness.

Non-clinical influences on decision taking in dermatology clinics
Andrew V. Fintushel, F M Hajaj, M S Salek, M K A Basra School of Medicine and Pharmacy, Cardiff University, Cardiff, Wales, UK
Many clinicians know that the process of taking clinical decisions is anything but straightforward. Although we accept that all decisions should be primarily be informed by scientific evidence, the reality of clinical medicine is extremely complex: the interweaving of evidence base with the particular circumstances and wishes of the individual patient along with the experience and wisdom of the clinician comprises the "art" of medicine. Given the central place of evidence taking in the raison d'être of the medical profession it is extraordinary how little attention has been paid to this in the literature. It was clear to us from our clinical experience that in reality a very wide range of influences, such as the clinician's perception of the patient's impairment of quality of life may play a role in clinical decision making, including many influences that are usually denied or at least not acknowledged. If these influences were better understood, it might be possible to train health care professionals to handle these influences more appropriately and hence improve the quality of clinical decision taking. The aim of our first study was to begin to understand this complexity among clinicians in Wales, seeking to identify the spectrum of non-clinical influences on clinical decision making in dermatology outpatient clinics. Ethical approval
was obtained. 46 dermatology clinicians (94% of those in Wales) from 9 different hospitals in Wales, UK were interviewed. The opening question was “According to your experience, what are the non-clinical influences on your decision making in dermatology?”. Interviews were recorded and analyzed. Non-clinical influences were either Patient-related, Physician-related or Practice-related. Patient-related factors included adherence to medication (reported by all 46 clinicians), concerns and worries of patient (46), quality of life (46), expectations (45), family and friends attitudes (40), age (38), financial status (30), place of residence (29), ethnicity (28), attitude and behavior (24), sex (24), time commitments (22), choice (11), and education and intelligence (9). Physician related influences included influence of colleagues (46), time constraints and work pressure (30) and influence of pharmaceutical companies (28). Practice-related influences included cost of treatment to Health Service (27), working in private practice v. Health Service (8), availability of treatment service (7) and bureaucracy in prescribing certain medications (4). In a second study, 61 patient consultations were observed and patients interviewed after, to gain the patients’ perspectives on the role of non-clinical influences on the decisions that had been taken concerning themselves. The insights of the patients were broadly similar to those revealed by dermatology clinicians in the previous study. It is often appropriate for clinicians to take into account non-clinical influences so that decisions are taken in the best interests of a specific patient; these are “good” influences. However many influences were not necessarily appropriate: the “bad” influences. Such inappropriate non-clinical influences might include age, financial status, place of residence, ethnicity, attitude, sex, education, time constraints and influence of pharmaceutical companies. National guidelines seek to improve the quality of clinical decision taking by being evidence based. However in reality guideline advice co-exists with often unrecognized non-clinical influences. If clinicians had greater understanding of the processes involved in decision taking it might be possible to develop strategies to recognize and neutralize the inappropriate influences. Greater understanding of this aspect of decision taking is necessary for evidence based decision taking to become a reality.