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4th International Workshop for the Study of Itch

San Francisco, California, USA
September 9–11, 2007

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Sunday, September 9, 2007 PM

3–6 pm Registration, set up posters
4–6 pm IFSI Board meeting
7–10 pm Welcome Reception

Monday, September 10, 2007 AM: Oral pres. OP1–OP6

8:30–8:45 Greeting and Introduction: *Earl Carstens,* Davis
Greeting: *Leo Chalupa*, Davis
IFSI Presidential Report: *Gil Yosipovitch,* Winston-Salem
8:45–9:00 Itch-related Research at the National Institute of Arthritis and Musculoskeletal and Skin Diseases: *Stephen Katz*, NIAMS/ NIH

Overview

9:00–9:30 The Puzzle of Itch: *Hermann O. Handwerker*, Germany
9:30–9:50 Itch and Pain: *Martin Schmelz*, Germany
9:50–10:10 Epidemiology of Chronic Itch and its Effect on Quality of Life: *Gil Yosipovitch*, Winston-Salem
10:10–10:30 Evidence-based Medicine and Pruritus: *Elke Weisshaar,* Germany
10:30–10:50 COFFEE BREAK/ POSTERS

Itch Classification

10:50–11:10 Itch Classification: *Jeffrey D. Bernhard*, Worcester
11:10–11:30 IFSI – Clinical Classification of Itch, Version 1.0: *Sonja Ständer*, Germany
11:30–12:00 Discussion
12:00–1:00 LUNCH

Monday, September 10, 2007 PM: Oral pres. OP7–OP17

Itch Genetics

1:00–1:20 Influence of Genotype, Dose and Sex on Pruritogen-induced Scratching Behavior in the Mouse: *Jeffrey Mogil,* Canada

Scalp Itch

1:20–1:40 How Does Your Scalp Feel? A Brief History of Scalp Somatosensory Mechanisms, From the Bad to the Good…: *Francis McGlone*, Unilever, UK

Neuropathic Itch

1:40–2:00 Mechanisms and Treatment of Neuropathic Itch and Pain: *Ralf Baron,* Germany
2:00–2:20 Neuropathic Itch in Patients and Rodent Models; A Systems Approach to Mechanisms: *Anne Louise Oaklander,* Florida

Systemic Disease

2:20–2:40 Pruritus in HIV Disease: *Tim Berger*, San Francisco
2:40–3:00 What are the New Studies Telling us About Pathophysiology of Uremic Pruritus: *Thomas Mettang,* Germany
3:00–3:20 COFFEE BREAK/ POSTERS
3:20–3:40 Update on the Pruritus of Cholestasis: *Nora Bergasa,* New York
3:40–4:00 Possibility for New Antipruritic Agent, Nalfurafine Hydrochloride (TRK-820), in Primary Biliary Cirrhosis: *H. Umeuchi,* Toray Industries, Japan
4:00–4:20 Confirmatory Study of TRK-820, Kappa Opioid Receptor Agonist, against Pruritus Resistant to the Currently Available Treatment in Hemodialysis Patients: *Kenji Takamori,* Japan

Psoriasis and itch

4:20–4:40 Vulvar Pruritus and Burning Sensation in Women Suffering from Psoriasis: *Jacek Szepietowski,* Poland
4:40–5:00 Psychophysiological Stress Mechanisms of Itch in Patients with Psoriasis: *EWM Verhoeven*, Holland

Tuesday, September 11, 2007 AM: Oral pres. OP18–OP27

Molecular aspects of itch

8:30–8:50 TRP Channels in Itch and Pain: *Makoto Tominaga*, Japan
8:50–9:10 Molecular Mechanisms of Itch in the Spinal Cord: *Zhou-Feng Chen*, St. Louis
9:10–9:30 Molecular Mechanisms of Neurogenic Inflammation and Pruritus: *Martin Steinhoff,* Germany
9:30–9:50 Involvement of Primary Afferents Expressing Voltage-Dependent Ca^{2+} Channel $\alpha_2\delta$-1 Subunit in Cutaneous Allergic Itch in Mice: *Yasushi Kuraishi*, Japan
9:50–10:10 The Activation of TP Prostanoid Receptor Induces Itch-associated Responses in Mice: *Tsugunobu Andoh*, Japan
10:10–10:30 COFFEE BREAK/ POSTERS

Itch pathways: monkey

10:30–10:50 Neural Mechanisms of Itch in Primate: *Robert LaMotte*, New Haven
10:50–11:10 Afferent nerve fibers mediating the sensation of itch: *Matthias Ringkamp*, Baltimore
11:10–11:30 Responses of primate spinothalamic tract neurons to itch producing stimuli: *Glenn Giesler, Jr.,* Minneapolis
11:30–11:50 Pharmacological studies of opioid-induced itch in monkeys: *M.C. Ko*, Ann Arbor

ADV Update

11:50–12:00 The New Itch Section in Acta Dermato-Venereologica: *Elke Weisshaar, Agneta Andersson*, Germany, Sweden
12:00–1:00 LUNCH

Tuesday, September 11, 2007 PM: Oral pres. OP28–OP37

Imaging Itch

1:00–1:20 Brain Networks of Itch and Scratch: *Gil Yosipovitch* Winston-Salem

Itch Treatment

1:20–1:40 Hyper- and Hypo-sensitivity to Histamine in Atopic Dermatitis: The Effect of Topical Anti-inflammatory Therapies on Sensitization: *Akihiko Ikoma*, Japan
1:40–2:00 Overview: Serotonergic and Opiate Drugs to Treat Itch: *Elke Weisshaar*, Germany
2:00–2:20 Antipruritic Potency of Serotonin Re-uptake-inhibitors: Results of a Proof-of-concept Study: *Sonja Ständer*, Germany
2:20–2:40 Evaluation of Antipruritic Therapy in a Large Collective of Pruritic Patients: Results of a Retrospective Study in 385 Patients: *Dorothee Siepmann,* Germany
2:40–3:00 Release of growth factors in human skin: *Roman Rukwied, Germany*
3:00–3:20 COFFEE BREAK/ POSTERS

Psychological and social aspects

3:20–3:40 Psychosocial Aspects of Itch – Somatoform Pruritus: *Uwe Gieler,* Germany
3:40–4:00 Itch and Mental Distress Among Adolescents. Preliminary Results From a Cross-sectional Study: *J.A. Halverson*, Norway
4:00–4:20 The Role of Attentional Focus and Interpretation of Bodily Sensations on Itch Sensitivity: AIM *van Laarhoven,* Holland
4:20–4:40 The Influence of Itching on Atopic Dermatitis Patients' Well-being: *Adam Reich,* Poland
4:40–4:50 Handwerker Prize sponsored by Beiersdorf

POSTERS

P1: Endothelin-Converting Enzyme-1 Degrades Substance P in Endosomes to Regulate Resensitization of the Neurokinin 1 Receptor. *D. Roosterman, G. S. Cottrell, B. E. Padilla, L. Muller, N. W. Bunnett, M. Steinhoff*

P2: ECE-1 Regulates rReceptor Recycling-independent Resensitization. *Dirk Roosterman, Graeme S. Cottrell, Benjamin E. Padilla, Nigel W. Bunnett, Martin Steinhoff*

P3: Agonist-induced Endocytosis of Rat Somatostatin Receptor 1. *Dirk Roosterman, Wolfgang Meyerhof, Martin Steinhoff*

P4: The Potential of Modern Chromatographic-Mass Spectrometric Techniques Applied To Itch Mediator Investigation. *Iain A. Fairweather, David Reilly, Francis McGlone*

P5: Possible Involvement of Lipoxin A_4 in Itch-associated Response of Mosquito Allergy in Mice. *Tasuku Nakano, Tsugunobu Andoh, Kiyoshi Kamimura, Yasushi Kuraishi*

P6: Electron Microscopic Study on Sprouting of Nerve Fibers into Epidermis of Dry Skin Mice. *Kenji Abe, Hiroshi Ito, Akira Yamasaki, Tsugunobu Andoh, Yasushi Kuraishi, Hiroshi Nojima*

P7: Cessation of Repeated Morphine Enhance Histamine- and Serotonin-induced Scratching Responses in Mice. *Kenji Abe, Emika Ohkoshi, Yuichi Fujii, Masago Ishikawa, Hiroshi Nojima*

P8: Intracisternal Morphine-induced Facial Scratching and Analgesia are Regulated Different μ-opioid Receptor Splice Variants in Mice. *Mitsuhiro Konno, Tsugunobu Andoh, Yuki Yamazaki, Tomomi Yamaguchi-Miyamoto, Yasushi Kuraishi*

P9: Antipruritic Effects of Nalfurafine, the Kappa Opioid Receptor Agonist. *Saadet Inan, Alan Cowan*

P10: Similar Patterns of Activity-dependent Slowing of Conduction Velocity in C Fibers of Humans and Pig. *O. Obreja, M. Ringkamp, E. Forsch, R. Rukwied, A. Klusch, M. Petersen, M. Schmelz*

P11: Responses and Modulation of Monkey Spinothalamic Tract Neurons to Itch-producing and Itch-inhibiting Stimuli. *Steve Davidson, Xijing Zhang, Sergey G Khasabov, Donald A Simone, Glenn J Giesler Jr.*

P12: Low Percentage of Potential Itch-signaling Superficial Spinal Neurons Project in Spinothalamic or Spinoparabrachial Pathways in Rat. *A.W. Merrill, M. Iodi Carstens, E. Carstens*

P13: Descending Control of Itch Sensation by 5-HT Neurons. *Yan-Gang Sun, Zhou-Feng Chen*

P14: The Activation of Brain Networks During Scratching. *Yozo Ishiuji, Tejesh Patel, Robert C. Coghill, Maria Isabel Hicks, Robert Kraft, Yoshitetsu Oshiro, Erica Winnicki, Gil Yosipovitch*

P15: Involvement of Proteinase-activated Receptor-2 in Spontaneous Scratching of Mice with Atopy-like Dermatitis. *K. Tsujii, T. Andoh, J. B. Lee, Y. Kuraishi*

P16: Development of Atopic Dermatitis-like Scratching Model in Hairless Mice and Analyses of its Pathophysiologic Mechanisms. *Masanori Fujii, Takeshi Nabe, Shigekatsu Kohno*

P17: The Brain Processing of Pruritus in Atopic Dermatitis. *Yozo Ishiuji, Robert C. Coghill, Tejesh Patel, Robert A. Kraft, Yoshitetsu Oshiro, Gil Yosipovitch*

P18: Involvement of Keratinocyte-derived Semaphorin 3A in Epidermal Innervation of Atopic Dermatitis. *Kenji Takamori, Mitsutoshi Tominaga*

P19: Possible Roles of Epidermal Opioid Systems in Pruritus of Atopic Dermatitis. *Mitsutoshi Tominaga, Kenji Takamori*

P20: Clinical Characteristics of Itching in Adult Patients Suffering from Atopic Dermatitis. *Adam Reich, Danuta Chrostowska-Plak, Jacek C Szepietowski*

P21: Nerve Fiber Distribution in Lichen Amyloidosis . *Ben Maddison, Lena S. Samuel, Julio Sanchez, Rita Pichardo, Gil Yosipovitch*

P22: Small Fiber-neuropathy as Possible Cause for Chronic Pruritus. *D. Siepmann, E. Pogatzki-Zahn, M. Marziniak, S. Ständer*

P23: Clinical Evaluation of a Large Collective of Patients with Chronic Pruritus: Subgroups, Underlying Diseases and Co-factors. *F. Sommer, P. Hensen, B. Böckenholt, D. Metze, T.A. Luger, S. Ständer*

P24: Pitfalls of Diagnosing and Treating Itch. *Elke Weisshaar*

P25: Negative Influence of Itching on Psoriatic Patients' Well-being. *Adam Reich, Ewa Hrehorow, Jacek C Szepietowski*

P26: Acne Itch: Is it a Real Problem for Patient with Acne? *Adam Reich, Katarzyna Trybucka, Anna Tracinska, Dominik Samotij, Blazej Jasiuk, Marek Srama, Jacek C Szepietowski*

P27: The Role of Inflammation and Hepatitis Virus Infection in Uremic Pruritus. *Yen-Ling Chiu, Yu-Seng Peng, Kwan-Yu Hung, Tun-Jun Tsai*

P28: Supplementation of Diamine-oxidase: – A New Approach in the Treatment of Histamine Intolerance. *M. Haeberle*

P30: Psychological aspects of itch. Qualitative research on older adults living with atopic dermatitis since childhood.
Shelley F. Diamond

ABSTRACTS: Oral Presentations (OP1-OP37)

THE PUZZLE OF ITCH *(OP1)*

Hermann Otto Handwerker; University of Erlangen/Nuremberg, Germany

Itch is one of the most enigmatic sensations for the psychophysiologist and a tantalizing problem for patients and their physicians. Over the last century several hypotheses were tried to explain itching. From the experiences of differential nerve blocks and from lesions of the anterolateral quadrant of the spinal cord it has become clear that the peripheral apparatus for itching must consist of slowly conducting unmyelinated and thinly myelinated nerve fibers connected to a central pathway closely associated to that for pain. fMRI studies confirmed this close association but also subtle differences. It remained controversial, however, if a specific subset of small nerve fibers mediates itch in the body periphery, or if a particular pattern of excitation is required. For histamine-related itching this question was decided a few years ago in favour of a specific group of unmyelinated, mechano-insensitive cutaneous nerve fibers which are also characteristic for mediating an extended axon reflex flare around a stimulated skin spot where a wheal indicates the action of histamine and other mediators released from mast cells. However, there are other forms of itching which are not related to wheal and flare reactions. An example is itching mediated by cowhage. In a recent microneurographic study we have shown that this type of itching does not excite the histamine-sensitive itch fibers, but polymodal mechanosensitive C-fibers besides A-delta fibers. Since these polymodal nociceptors are also responsive to various algogenic substances, the question of the peripheral and central pathway for this type of itch remains enigmatic. Another salient question is whether the different forms of itch perceptions apparently subserved by different peripheral and possibly also central nervous apparatus are distinct. The implications of these new findings for differentiating clinically important forms of pruritic diseases will be discussed in this lecture.

ITCH AND PAIN *(OP2)*

Martin Schmelz; Department of Anaesthesiology Mannheim, University of Heidelberg, Germany

Antagonistic interaction between pruritus and pain as well as similarities in peripheral and central sensitization processes have been described. It is common experience that the itch sensation can be reduced by the painful sensations caused by scratching. Vice versa analgesia may reduce this inhibition and thus enhance itch. On the other hand, itch and pain exhibit corresponding patterns of central sensitization. After histamine sensitive pruriceptors were discovered among mechano-insensitive C-fibers the neurophysiological basis for the itch sensation appeared to be solved. However, latest results on new itch fibers have added complementary perspectives for the neuronal basis of itch. Activation patterns of mechano-insensitive C-nociceptors and polymodal nociceptors by endothelin will be presented that indicate that the mixed sensation of pain and itch induced by endothelin may not only be based on the activation of specific pruriceptive nerve fibers. We observed lasting activation of polymodal nociceptors in humans by endothelin injection. This activity may also contribute to the itch sensation induced by endothelin. Possible mechanisms of itch induction other than by "labelled line" pathways will be presented.

EPIDEMIOLOGY OF CHRONIC ITCH AND ITS EFFECT ON QUALITY OF LIFE *(OP3)*

Gil Yosipovitch MD; Department of Dermatology, Wake Forest University Health Sciences, Winston Salem NC, USA

There is a paucity of epidemiological studies addressing the extent of chronic itch and its effect on quality of life in both the population as a whole as well as in skin diseases and systemic disease. Recent studies suggest that this symptom is common. A large cross ssectional study in Oslo in more than 18,000 adults reported that 8% of the population suffers from itch and that chronic pain was associated with itch. The largest and most recent epidemiological study in 18,000 hemodialysis patients found that 42% of the patients suffered from chronic itch. It had a significant impact on the quality of life of these patients, moreover it was associated with a 17% higher mortality risk associated to sleep quality. Many variables may affect the prevalence and quality of life of chronic itch patients such as socioeconomic status , ethnicity and psychological factors. The precise nature of these associations require further investigation.

EVIDENCE-BASED MEDICINE AND PRURITUS *(OP4)*

Elke Weisshaar; Clinical Social Medicine, Occupational and Environmental Dermatology, University Hospital Heidelberg, Germany

Clinical expertise and experiences of physicians are of inestimable value. Many physicians base clinical decisions on an understanding of the aetiology and pathophysiology of disease and logic. This paradigm is sometimes problematic because accepted hypothesis change over time. Evidence-based medicine links and integrates clinical research with clinical practise. Ideally, whenever a clinical question has no satisfactory answer it should be addressed by clinical research. Confirmatory studies are needed and systematic reviews can be used to summarise study results. Even the best evidence has limitations in individual patients with complicated disease courses or in multifactorial symptoms such as pruritus. In consideration of barriers and limitations it can be demonstrated in some forms of pruritus e.g. uraemic pruritus, cholestatic pruritus, pruritus in the elderly that an approach to evidence-based medicine is helpful and necessary.

ITCH CLASSIFICATION *(OP5)*

Jeffrey D. Bernhard, MD; Journal of the American Academy of Dermatology, Worcester, Massachusetts, USA

According to Erasmus, thanks to folly, there are as many grammars as there are gramarians. This will not be the case when it comes to the clinical classification of itch. Under the leadership

of Dr Sonja Ständer, members of the International Forum for the Study of Itch worked together, largely through e-mail, to develop a provisional clinical classification of itch, which has just been published (Ständer S, Weisshaar E, Mettang T, Szepietowski JC, Carstens E, Ikoma A, Bergasa NV, Gieler U, Misery L, Wallengren J, Darsow U, Streit M, Metze D, Luger TA, Greaves MW, Schmelz M, Yosipovitch G, Bernhard JD. Clinical classification of itch: a position paper of the international forum for the study of itch. Acta Derm Venereol 2007; 87: 291–294). As the IFSI classification is test-driven in clinical practice and as discoveries and discussion continue, it will be revised, fine-tuned, and improved. Dr Ständer will be happy to receive your advice.

IFSI – CLINICAL CLASSIFICATION OF ITCH, VERSION 1.0 *(OP6)*

S. Ständer, E. Weisshaar, T. Mettang, J.C. Szepietowski, E. Carstens, A. Ikoma, N.V. Bergasa, U. Gieler, L. Misery, J. Wallengren, U. Darsow, M. Streit, D. Metze, T.A. Luger, M.W. Greaves, M. Schmelz, G. Yosipovitch, J. D. Bernhard; *Department of Dermatology, University of Münster, Germany*

Chronic itch is a common and distressing symptom that arises from a variety of skin conditions and systemic diseases. Despite this, a clinically based classification of pruritic diseases to assist in the diagnosis and cost-effective medical care of patients suffering from pruritus did not exist. Recently, many members from IFSI proposed in a consensus paper a classification focusing on clinical signs and distinguishes between diseases with and without primary or secondary skin lesions (Acta DermVenereol 2007; 87: 291–294). Three groups of conditions are proposed: pruritus on diseased (inflamed) skin (group I), pruritus on non-diseased (non-inflamed) skin (group II), and pruritus presenting with severe chronic secondary scratch lesions like prurigo nodularis (group III). The next part classifies the underlying diseases according to different categories: dermatological diseases, systemic diseases including diseases of pregnancy and drug-induced pruritus, neurologic and psychiatric diseases. In some patients more than one cause may account for pruritus (category "mixed") while in others no underlying disease can be identified (category "others"). This classification is meant to serve as a diagnostic route for better evaluation of patients suffering from chronic pruritus and aims helping to improve patients' care. Interestingly, the discussion leading to the first version of the classification showed that clinically applied terms are used different in several countries. Especially the term pruritus sine materia provoked much discussion. Accordingly, clinical terms need to be re-defined to describe various forms of chronic pruritus. The aim of the current discussion is an international standardized terminology of chronic pruritus.

INFLUENCE OF GENOTYPE, DOSE AND SEX ON PRURITOGEN-INDUCED SCRATCHING BEHAVIOR IN THE MOUSE *(OP7)*

Jeffrey S. Mogil; Dept. of Psychology and Centre for Research on Pain, McGill University, Montreal, QC, Canada

Itch features considerable interindividual variability in humans, and initial studies using animal models have demonstrated a likely role of genetic factors in mediating such variability. In an attempt to systematically study genetic mediation of itch in the mouse such that gene identification by linkage mapping might be achieved, we examined scratching behavior induced by histamine and chloroquine in mice of 11 inbred mouse strains. Multiple chloroquine drug doses were used, revealing the existence of inverted-U dose-response relationships in every strain, allowing us to determine strain-dependent peak scratching behavior over the entire dose range. Peak chloroquine-induced scratching varied by 2.5-fold in this set of strains; scratching behavior shows moderate heritability in the mouse. The present data also reveal, for the first time, significant sex differences in pruritogen-induced scratching behavior, with female mice scratching an average of 23% more than males. Finally, a comparison of the strain means obtained here with previously collected data using nociceptive assays revealed a suggestive negative genetic correlation between chloroquine-induced itch and thermal pain, such that strains sensitive to pain are resistant to itch and vice-versa. This finding may have implications both for our understanding of itch pathophysiology and for the identification of itch-related genes. This work was supported by the NIH (DA15191), the Canada Research Chairs Program, and the Canada Foundation for Innovation.

HOW DOES YOUR SCALP FEEL? A BRIEF HISTORY OF SCALP SOMATOSENSORY MECHANISMS, FROM THE BAD TO THE GOOD…. *(OP8)*

Francis McGlone[1,2], Martin Schmelz[3]; [1]Unilever R&D, Bebington; [2]Dept. Neurological Sciences, Liverpool University, UK; [3]Dept. Anesthesiology and Intensive Care Medicine, Faculty of Clinical Medicine, Mannheim, Germany

As a sensory modality cutaneous sensation is highly heterogeneous, with different body sites displaying as wide range of sensitivity to touch, temperature, pain and itch – the four main sub-modalities sensed by the skin – with increasing evidence that a fifth modality exists in human skin that is responsible for pleasant tactile experiences. This variation in sensitivity, at the neurobiological level, is dependent upon skin biology, innervation density and receptor sub-type, and at the central level on processes of 'within-modality' multi-sensory integration and affective represe Scalp skin provides a perfect example of this sensory heterogeneity, and in this presentation we will review recent studies employing a range of techniques from quantitative sensory testing (QST) and intradermal microdialysis (IDM), to behavioural measures and functional magnetic resonance imaging (fMRI), that are providing us with a better understanding of the sensory, perceptual and emotional properties of the scalp in normal and abnormal conditions, with a focus on mechanisms mediated by sub-populations of afferent c-fibres that encode negative (itch) and positive (pleasure) scalp sensations.

MECHANISMS AND TREATMENT OF NEUROPATHIC ITCH AND PAIN *(OP9)*

Ralf Baron; Division of Neurological Pain Research and Therapy, Department of Neurology, University of Kiel, Germany

Lesions in the peripheral and central nervous system may lead to neuropathic itch (e.g., postherpetic neuralgia, chemotherapy

induced neuropathy, HIV-neuropathy, notalgia paresthetica, brachioradial pruritus, multiple sclerosis). Itch sensations are conveyed by specialized unmyelinated primary afferents and spinothalamic projection neurons. In the spinal cord ongoing input of pruritoceptive C-fibers provokes fundamental secondary changes in the excitability of the dorsal horn neurons (central sensitization). With central sensitization a dramatic change in the perception of somatosensory stimuli occurs. Primary afferent A-fibers that normally convey non-noxious information gain access to pruritoceptive dorsal horn neurons. Thereby, light touching and pinprick stimuli around an itching site evoke pruritus (alloknesis, hyperknesis). There is a remarkable similarity between the phenomena associated with central sensitization in itch and pain. Nociceptor activity leads to pain and also sensitizes neurons in the dorsal horn. With nociceptive central sensitization A-fiber input induces brush-evoked allodynia and hyperalgesia that are characteristic features of neuropathic pain states. Since mechanisms of central sensitization considerably contribute to the amplification of itch and to the chronicity of pruritic skin disorders, molecular structures involved in central sensitization are interesting therapeutic targets. The similar patterns of central sensitization in itch and pain have led to the use of drugs well known from pain therapy. Gabapentin and pregabalin act on voltage-dependent Ca-channels located on synaptic terminals of primary afferent neurons in the dorsal horn and thereby sooth central sensitization. First uncontrolled studies show efficacy of these compounds in chronic itch.

NEUROPATHIC ITCH IN PATIENTS AND RODENT MODELS; A SYSTEMS APPROACH TO MECHANISMS *(OP10)*

A.L. Oaklander, J.W. Lee, K.L. Brewer, R.P. Yezierski; Harvard Medical School, Brody School of Medicine, East Carolina University, University of Florida, Florida, USA

Neuropathic itch (NI) is chronic pathological itch caused by neural injury rather than pruritogenic stimuli. Because it goes unrecognized by most physicians, clinical information is scant, mechanisms are unknown, and treatment is largely ineffective. NI has been associated with spinal root compression (notalgia paresthetica), shingles, and small-fiber polyneuropathy. Some but not all NI patients have neuropathic pain as well. Patients with co-localizing NI and severe sensory loss risk self-injury from scratching desensate skin. Spinal-cord cavernous hemangiomas have been specifically associated with central NI. A dorsal spinal location and hemosiderin rim may predispose them to cause chronic dermatomal NI. We have hypothesized that injections of quisqualate (QUIS) into the dorsal horn of rats models this type of central NI. Following intramedullary QUIS injection, some rats excessively groom the dermatome corresponding to the spinal segment of injection and develop ulcers on their flanks (overgroomers). We are correlating behavioral and pathological data from adult Sprague Dawley rats with lower thoracic QUIS-injections to test hypotheses about NI pathogenesis. Skin and spinal cord tissues have been sampled at sacrifice of overgrooming and non-grooming QUIS-injected rats. Skin sections have been immunohistochemically labeled with antibody against PGP9.5 to permit measurements of total axonal length. Our data suggest that intramedullary QUIS injections cause a central-peripheral distal axonopathy (CPDA) with reduced cutaneous innervation. Overgroomers had less remaining cutaneous innervation than non-groomers ($p = 0.02$). The longitudinal extent of dorsal-horn lesions did not correlate with the presence of overgrooming, nor with the magnitude of cutaneous neurite losses. Perhaps central spinal NI involves peripheral as well as central neural injury?

PRURITUS IN HIV DISEASE *(OP11)*

Timothy Berger, MD; University of California, San Francisco, USA

The content of this abstract is based on clinical experience and anecdotal observation, and hence is opinionated. No specific studies have been done in HIV-infected patients to understand the neurophysiology of their pruritus and whether it is different than patients without HIV disease. Pruritus is a common complaint of patients with HIV disease. It is a marker of HIV infection, usually when the CD4 count is below 200, and when viral load is high – when patients enter the risk window for opportunistic infections. HIV pruritic conditions tends to resolve with adequate HAART (anti-HIV treatment), and relapse when treatment fails, and thus may be an indirect marker of the effectiveness of HAART in an individual patient. Virtually all pruritus in patients with HIV is related to an inflammatory skin disease. HIV itself, HIV neuropathy, and HIV myelodysplasias and lymphoma rarely if ever are the cause of pruritus. The pruritic conditions primarily affecting patients with HIV include drug eruptions, eosinophilic folliculitis (EF), insect bite hypersensitivity, atopic-like dermatitis, xerosis and xerotic eczema, photodermatitis, prurigo nodularis, and eczematous seborrheic dermatitis/sebopsoriasis. Patients often have multiple conditions simultaneously. Secondary infection with *S. aureus* is common. These conditions are managed with standard treatments with success. EF uniquely responds to itraconazole, isotretinoin, and at times topical permethrin. Except for EF and atypical sebopsoriasis, the pruritic conditions seen in patients with HIV disease are very similar to those seen in the elderly, and are hypothesized to be related to loss of effective TH1 function and subsequent TH2 dominance in the cutaneous immune system.

WHAT ARE THE NEW STUDIES TELLING US ABOUT PATHOPHYSIOLOGY OF UREMIC PRURITUS *(OP12)*

Thomas Mettang; Department of Nephrology, Deutsche Klinik für Diagnostik, Wiesbaden, Germany

Until now the cause of uremic pruritus is still unknown. Many metabolic, hormonal and neurological derangements occurring in chronic kidney disease have been suspected and most of them have been ruled out as essential contributors in the pathogenesis of renal itch. New insights mainly come from partially effective medical or physical therapeutic approaches. One of the hot topics in this respect is treatment with μ-opioid-receptor-antagonists (such as naltrexone or nalmefene) and kappa–opioid-agonists (such as nalfurafine, etc), both groups of substances seem to reduce itch not only in uremic state suggesting a general impact of central or peripheral opoid-receptors in the perception of itch. Likewise compounds targeted against central and/or peripheral

neuropathy such as gabapentin may also lower the torture of uremic pruritus. Anti-inflammatory immune-modulating drugs such as tacrolimus, thalidomide or pentoxfylline have also been shown to be effective in reducing uremic pruritus while at the same time a series of studies have shown up-regulated inflammatory mediators in these patients. Even topical treatment with gamma-linolenic acid alleviated uremic pruritus in otherwise refractory cases. The question remains how to put all these results into perspective and combining them to a comprehensive pathophysiological concept.

UPDATE ON THE PRURITUS OF CHOLESTASIS *(OP13)*

Nora V. Bergasa, MD; Woodhull Medical Center, Brooklyn, NY

Pruritus is a complication of cholestasis. Not all patients with cholestasis itch, which may be explained, in part, by the presence of single nucleotide polymorphisms (SNP)s in relevant genes including the SNP V1188E in exon 25 of the multidrug resistance protein 2 gene, found in19% of patients with PBC and pruritus from the USA and Italy, and the SNP A118G in Exon-1 of the OPRM1 gene, which codes for the μ-opioid receptor, to which morphine binds, in 29% of samples from patients with PBC and with pruritus, but in 40% of the group from the USA. Increased opioidergic neurotransmission contributes to the pathogenesis of the pruritus of cholestasis; therefore, SNPs in the OPRM1 gene may have relevance in the perception of pruritus. The drug gabapentin has antinociceptive properties. In a double-blind randomized placebo-controlled study in patients with liver disease and pruritus this drug was associated with increased scratching activity, the behavioral manifestation of pruritus, in contrast to the placebo, which was associated with a decrease. Dopamine was reported to mediate the placebo effect in Parkinson's disease, and gabapentin decreases the release of dopamine; thus, gabapentin may have prevented the placebo effect mediated by the placebo intervention in this study. In this context, haloperidol, an agonist at the dopamine receptor 2, was reported to ameliorate the pruritus caused by increased opioidergic tone mediated by morphine, which would be analogous to the pruritus of cholestasis. Thus, it is plausible that the antipruritic effect of the placebo resulted from the activation of dopamine neurons from dopamine release stimulated by the placebo intervention. The strong placebo effect documented in this study emphasizes the need to incorporate behavioral methodology in studies of pruritus.

POSSIBILITY FOR NEW ANTIPRURITIC AGENT, NALFURAFINE HYDROCHLORIDE (TRK-820), IN PRIMARY BILIARY CIRRHOSIS *(OP14)*

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Pruritus is a common symptom in primary biliary cirrhosis (PBC) although the pathogenesis remains unclear. In this study, the peripheral concentration of opioid peptides, in addition to histamine and IgE levels, in 59 patients with PBC were investigated. The histamine and IgE levels were not related to patient with/without pruritus. However, the plasma concentration of μ-opioid peptides such as endomorphin-1 and beta-endorphin in PBC patients with pruritus were significantly higher than these in patients without pruritus (p=0.004, p=0.010, respectively). Those data indicated the involvement of μ-opioid system on itch pathway in pruritus with PBC rather than histamine system. According to the recent studies, kappa-opioid system produces many opposite effect to μ-opioid system, indicating the possibility that the activation of kappa-opioid system exert antipruritic effect. Nalfurafine hydrochloride (TRK-820) has a unique chemical structure and an agonistic activity to kappa-opioid receptor. Nalfurafine was effective to spontaneous scratching behavior in MRL/lpr mice, an autoimmune diseases (PBC) model. Taken together, nalfurafine has potential therapeutic values against μ-opioid system related-pruritus with PBC and is likely to reduce itch sensation itself in a new concept.

CONFIRMATORY STUDY OF TRK-820, KAPPA OPIOID RECEPTOR AGONIST, AGAINST PRURITUS RESISTANT TO THE CURRENTLY AVAILABLE TREATMENT IN HEMODIALYSIS PATIENTS *(OP15)*

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TRK-820 is a novel selective kappa agonist confirmed to produce intensive antipruritic effects. This time, soft capsules of TRK-820 were administered once daily via oral route for 14 days in 337 hemodialysis patients with pruritus which had been resistant to the currently available treatments, and the efficacy was assessed by a multicenter double-blind comparative study at 73 medical institutions in Japan. In terms of the change observed in VAS (Visual Analogue Scale) before and after the product administration, the difference between the placebo group and 5 μg dose group was 8.26 mm (95% confidence interval: [3.05, 13.47], p=0.0010, 2.5% one-sided test), and the efficacy of the product was confirmed. In addition, antipruritic effects were also observed in 2.5 μg group as well (p=0.0005). The major adverse drug reactions were insomnia, constipation and sleepiness. However, there was no adverse reaction which could be problematic in the clinical use. Based on these results, the efficacy of TRK-820 was confirmed, and it was shown that the practical use of this product would be possible as a drug which is effective against persistent pruritus in patients with hemodialysis.

VULVAR PRURITUS AND BURNING SENSATION IN WOMEN SUFFERING FROM PSORIASIS *(OP16)*

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Psoriasis is a chronic inflammatory skin disease. Approximately 80% of psoriatic individuals experience pruritus of different intensity. The aim of the study was to evaluate the frequency of vulvar discomfort (pruritus and burning of the vulva) in women suffering from psoriasis, and how these symptoms influence patients' social well-being and psyche. Ninety-three female women with psoriasis were included in the study. Clinical severity of psoriasis was assessed according to the Psoriasis Area and Severity Index. The intensity of vulvar discomfort, considered as itching or burning sensation of the vulvar area, was evaluated by Visual Analog Scale (VAS), and the mood by Beck's Depression Inventory (BDI). Psoriatic lesions on the vulva were found in 26.9% of all included women. At the time of examination 44.1% participants reported vulvar discomfort. 19.4% females declared the feeling of itching, 10.8% burning sensation and the remaining 13.9% patients both itching and burning. The mean intensity of vulvar discomfort was 3.8±2.6 points. No significant correlation was found between discomfort intensity and severity of psoriasis (p=0.3). However, patients suffering from vulvar itching or burning significantly more often had psoriatic lesions on the vulva compared to patients without these symptoms (42.8% vs. 3.9%, p<0.001). In addition, women reporting vulvar discomfort had also higher scoring in BDI compared to women free from vulvar discomfort (15.2 vs. 11.3, p=0.02), suggesting the itching or burning within vulva may predispose to depressive symptoms. In conclusion, vulvar discomfort is an important clinical problem in women suffering from psoriasis and should be taken into consideration during the care of psoriatic female patients.

PSYCHOPHYSIOLOGICAL STRESS MECHANISMS OF ITCH IN PATIENTS WITH PSORIASIS *(OP17)*

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Itch is a prominent feature of the disease activity of many skin diseases and about 80% of all patients with psoriasis report suffering from itch. The relationship between the disease activity in skin diseases and psychophysiological stress mechanisms has received increasing attention. With regard to the effects of psychological stressors on psoriasis, a majority of the patients (37% to 88%) believe in a relationship between perceived stressors and their disease activity. Additionally, several studies indicate that there might be a relationship between psychological stress factors and the itch sensation of psoriasis. For example, it has been reported that patients who experienced severe stressful events before an eruption of their psoriasis suffered from itch and this relation is assumed to be mediated by neuroendocrine and immunological parameters. The purpose of the present study was to examine the relationship between psychological stress factors and itch in 100 patients with psoriasis as well as the possible mediating role of endocrine and immunological mechanisms in this relationship. For this purpose, a prospective study of six months was performed with repeated assessments (weekly and monthly) of clinical (PASI), physiological (endocrine measures of cortisol and immunological measures of IL-1, IL-2, IL-4, IL-6, IL-10), and self reported data (e.g. experienced itch, experienced stressors). Preliminary results indicating a relationship between stressors and itch as well as the mediating role of endocrine and immunological parameters will be presented.

TRP CHANNELS IN ITCH AND PAIN *(OP18)*

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TRP channels were first described in *Drosophila*, where photoreceptors carrying *trp* gene mutations exhibited an abnormal transient responsiveness to continuous light. In mammals, TRP channels comprise six related protein families (TRPC, TRPV, TRPM, TRPA, TRPML, TRPP). Perhaps TRP channels are best recognized for their contributions to sensory transduction, responding to temperature, nociceptive stimuli, touch, osmolarity, pheromones and other stimuli from both within and outside the cell. Among the TRP ion channel super family, nine (TRPV1, TRPV2, TRPV3, TRPV4, TRPM2, TRPM4, TRPM5, TRPM8 and TRPA1) are thought to be activated by temperatures from cold to heat, thereby called thermosensitive TRP channels, although cold sensitivity of TRPA1 is controversial even after the analyses of mice lacking TRPA1. TRPV1, TRPV2, TRPM8 and TRPA1 are well expressed in the sensory neurons and believed to be involved in nociception or pain relief. Especially, TRPV1 and TRPA1 are expressed in unmyelinated C-fibers and known to be activated the various nociceptive stimuli in addition to temperatures. Involvement of TRPV1 in itch sensation was reported. In contrast to the heat- or cold-activated TRP channels, five other thermosensitive TRP channels are activated by warm temperatures and expressed in the tissues other than sensory neurons, suggesting that those TRP channels function at physiological body temperature. Especially, TRPV3 and TRPV4 are well expressed in the skin keratinocytes and thought to be involved in temperature detection at the skin. The two TRP channels could be involved in itch sensation in addition to the temperature detection.

MOLECULAR MECHANISMS OF ITCH IN THE SPINAL CORD *(OP19)*

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Chronic itch represents a significant clinical problem resulting from renal diseases and liver diseases, as well as several serious skin diseases such as atopic dermatitis. The molecular mechanims underlying itch sensation in the central nervous system, however, remains elusive. To identify molecules involved in itch and/or pain in the dorsal spinal cord, genome-wide dorsal/ventral spinal cord differential screenings were performed. One of the dorsal horn-enriched genes identified is gastrin-releasing peptide receptor (GRPR), which is a G protein-coupled receptor for GRP, a mammalian homolog of the amphibian bombesin-

like peptides. Expression of GRPR is restricted to lamina I of the dorsal spinal cord, whereas GRP is expressed in a subset of unmyelinated C-fiber sensory neurons. GRPR mutant mice showed comparable pain responses relative to wild-type mice. In contrast, induction of scratching behaviour was significantly reduced in GRPR mutant mice in response to pruritogenic stimuli. Intrathecal injection of a GRPR antagonist significantly inhibited scratching behaviour in several itch models. Moreover, intrathecal injection of neuromedin B (NMB), another bombesin-like peptide in mammals, induced scratching responses in mice, suggesting a role for NMB receptor in itch. Together, our data suggest that mammalian bombesin-like peptides and their receptors may represent a major component of the molecular machinery that is important for mediating itch sensation in the dorsal horn of the spinal cord. GRPR and other bombesin-like receptors may provide a central therapeutic target for antipruritic drug development.

MOLECULAR MECHANISMS OF NEUROGENIC INFLAMMATION AND PRURITUS *(OP20)*

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The presentation will highlight our knowledge about the role of the peripheral and central nervous system in neurogenic inflammation and pruritus, and focuses on recently attained neurophysiological, neuroimmunological and neuroendocrine insights into neuroimmune interactions and skin-derived pruritus that may affect future anti-inflammatory or anti-pruritic therapeutic strategies. Beside neuropeptides, special attention is paid to newly identified itch-specific neuronal pathways by proteases in the peripheral as well as central nervous system. In the periphery, a close interaction between neuropeptides, their receptors and endopeptidases is demanded for appropriate neuropeptide signaling. Accordingly, dysregulation between these molecules results in chronic inflammation, and probably chronic pruritus or pain. For example, endothelin-converting enzyme-1 (ECE-1) or neutral endopeptidase (NEP) control substance P degradation and thereby neurokinin-1 mediated signaling of inflammaton and/ or pruritus. Overexpression of ECE-1 results in decreased receptor desensitization which may influence SP-mediated activation of mast cells and mediator release during inflammation/pruritus. Newly identified or unduly neglected intracutaneous itch mediators such as proteases and relevant receptors such as interleukin-31 RA will be also discussed. In sum, the identification and characterization of new mediators, receptors and endopeptidases may open new avenues as anti-inflammatory and/ or anti-pruritic drugs that may also be beneficial for the treatment of chronic inflammatory skin diseases or pruritus.

INVOLVEMENT OF PRIMARY AFFERENTS EXPRESSING VOLTAGE-DEPENDENT CA^{2+} CHANNEL $\alpha_2\Delta$-1 SUBUNIT IN CUTANEOUS ALLERGIC ITCH IN MICE *(OP21)*

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Voltage-dependent Ca^{2+} channel $\alpha_2\delta$-1 subunit is expressed in primary afferents and may be a primary site of inhibitory action of the anticonvulsant gabapentin on neuropathic pain. We examined using ICR mice whether primary afferents expressing $\alpha_2\delta$-1 subunit would be involved in itch signaling. Intradermal injections of histamine (100 nmol/site) and an extract of mosquito salivary gland (10 μg/site) elicited scratching in healthy and sensitized mice, respectively. Gabapentin (3–30 mg/kg orally and 10–100 μg/site locally) produced dose-dependent inhibition of scratching elicited by the extract but not by histamine. Gabapentin (30 mg/kg orally) also suppressed the activity of cutaneous nerve branch increased by the extract in sensitized mice. Neonatal capsaicin treatment, which almost depleted TRPV1 immunoreactivity in the dorsal root ganglia, suppressed scratching elicited by the extract and histamine, but the inhibition (74%) of the former was significantly larger than the inhibition (30%) of the latter. In murine dorsal root ganglia, $\alpha_2\delta$-1 subunit was mainly expressed in neurons with a diameter of 15–20 μm and H_1 histamine receptor mainly in neurons with a diameter of 20–30 μm. Eighty-five percent of $\alpha_2\delta$-1 subunit-immunoreactive neurons were positive for TRPV1 capsaicin receptor, and 64% of TRPV1-immunoreactive neurons were positive for $\alpha_2\delta$-1 subunit. The results suggest that $\alpha_2\delta$-1 subunit and H_1 histamine receptor are expressed in different groups of primary afferents and that primary afferents expressing $\alpha_2\delta$-1 subunit and TRPV1 receptor are involved in signaling of cutaneous allergic itch.

THE ACTIVATION OF TP PROSTANOID RECEPTOR INDUCES ITCH-ASSOCIATED RESPONSES IN MICE *(OP22)*

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Thromboxane A_2 (TXA_2), a metabolite of arachidonic acid produced by cyclooxygenase and thromboxane synthase, produces biological action through TP receptor and is thought to participate in chronic dermatitis. The present study investigated the involvement of TXA_2 and TP receptor in cutaneous itch. An intradermal injection of U-46619, a stable analogue of TXA_2, elicited scratching, an itch-associated response, in mice. The action of U-46619 was inhibited by a co-injection of the TP receptor antagonist ONO-3708 and was abolished by TP receptor deficiency. TP receptor was mainly expressed in nerve fiber in the skin and keratinocytes. Thromboxane synthase was also expressed in the keratinocytes. U-46619 increased intracellular Ca^{2+} ion concentration in primary cultures of murine dorsal root ganglion neurons and keratinocytes. The results suggest that TXA_2 synthesized by keratinocytes acts as an itch mediator. It may elicit itch through the activation of TP receptors on primary afferents and keratinocytes; keratinocytes may produce itch mediators including TXA_2. Thus, thromboxane synthase inhibitor and TP receptor antagonists will be candidates for antipruritic medicines.

NEURAL MECHANISMS OF ITCH IN PRIMATE *(OP23)*

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Though itch is a fundamental sensory modality and can be a significant clinical problem, there is a great deal to learn about the neural mechanisms that enable itch to be encoded as a unique sensation and about the neural mechanisms that modulate itch. This presentation summarizes recent findings of an NIH-sponsored project to study the neural mechanisms of itch. Psychophysical measurements of pruritic and nociceptive sensations and dysesthesias evoked by cutaneous application of histamine or spicules of cowhage in humans were correlated with responses of peripheral nerve (PN) fibers and spinothalamic tract (STT) neurons to the same stimuli in monkeys. Monkeys exhibited site specific scratching to cowhage or histamine. In humans, histamine and cowhage each evoked a sensation of itch, typically accompanied by nociceptive sensations of burning and/or pricking/stinging and sometimes dysesthetic cutaneous areas of hyperalgesia, hyperknesis and alloknesis. The sensory effects of cowhage were shown not to be histamine-mediated. Subpopulations of polymodal nociceptive C- and A-delta PN fibers typically responded to cowhage and to histamine whereas STT neurons responded to either but not both. None of these was pruriceptive specific because they also responded to noxious mechanical, heat or chemical stimuli that are nociceptive to humans. Additionally, nociceptive specific PN fibers and STT neurons were identified as responding to noxious, but not the pruritic, stimuli. Of the neurons responding to pruritic stimuli, perhaps some may contribute to the nociceptive sensations evoked by pruritogens while others may contribute to itch but only in the absence of suppression by activity in the nociceptive specific neurons. *Supported by NIH grant P01 NS047399.*

AFFERENT NERVE FIBERS MEDIATING THE SENSATION OF ITCH *(OP24)*

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The peripheral neuronal mechanisms underlying non-histaminergic itch are not well understood. Previous studies demonstrate that mechanoinsensitive C fiber afferents (C-MIAs) mediate histamine-induced itch and skin reddening (flare). However, stimuli unlikely to activate C-MIAs (punctate mechanical and heat stimuli) can produce the sensation of itch in human. Furthermore, itch in human may not be accompanied by skin reddening. Together these findings indicate that other afferent nerve fibers besides C-MIAs exist that can mediate the sensation of itch. Anectodal studies in human report that spicules from the plant mucuna pruriens (cowhage) produce the sensation of itch without a flare reaction. To substantiate these earlier observations, a series of psychophysical studies in human were performed in which flare and itch sensation produced by cowhage were quantified, and the effect of topical antihistamine and capsaicin treatment on cowhage-induced itch was measured. In addition, recordings from primary afferent nerve fibers innervating the hairy skin of non-human primate were performed to investigate which nerve fibers are activated by cowhage spicules. In the psychophysical studies in human, cowhage spicules produced the sensation of itch in the absence of a flare response. Cowhage-induced itch was not affected by topical antihistamine treatment, but was abolished in skin pretreated with topical capsaicin. Electrophysiological recordings from afferent nerve fibers in non-human primate revealed that cowhage spicules activated mechano heat sensitive unmyelinated nerve fibers (C-MH) but not C-MIAs. In addition, small myelinated afferents could be activated by cowhage spicules. We conclude that cowhage induced itch in human is mediated through a non-histaminergic mechanism and involves the activation of capsaicin sensitive polymodal afferents.

RESPONSES OF PRIMATE SPINOTHALAMIC TRACT NEURONS TO ITCH PRODUCING STIMULI *(OP25)*

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We examined the responses of spinothalamic tract (STT) neurons to pruriceptive and nociceptive stimuli in monkeys. In the first study (Simone et al. 2004), STT neurons in the superficial and deep dorsal horn were antidromically activated from the ventral posterior lateral nucleus. Responses to innocuous and noxious mechanical stimuli as well as intradermal injections of capsaicin and histamine were determined. Seven of the eleven examined wide dynamic range neurons were activated by injections of histamine. The durations of the responses of several of these neurons matched the time course of the itch produced in humans by injection of comparable amounts of histamine. Only one of six tested high threshold STT neurons responded to histamine. Each of the neurons that was activated by histamine also responded, and often at higher frequencies, to noxious mechanical, thermal and chemical stimulation. These findings do not support the existence of "itch-specific" STT neurons in primates. In a second study (Davidson et al., 2005), primate STT neurons projecting to the posterior thalamus or VPL were examined for responses to histamine and to application of spicules from the non-histaminergic itch producing legume cowhage. Twenty of sixty examined STT neurons responded to one of the pruritic stimuli but none responded to both. This surprising result indicates that separate populations of STT neurons code pruritic responses to histamine and cowhage. The pruritic responses of several neurons were inhibited by scratching the receptive field, suggesting that the reduction of itch sensation produced by scratching results from inhibition of pruriceptive STT neurons. Itch-responsive STT neurons were found to project to several nuclei within the posterior thalamus and to VPL. This indicates that neurons within several thalamic nuclei receive and process pruriceptive information.

PHARMACOLOGICAL STUDIES OF OPIOID-INDUCED ITCH IN MONKEYS *(OP26)*

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Opioid analgesics have been widely used in the clinic. However, the most common side effect of spinal morphine administration

is itch/pruritus. Given that opioid receptor subtypes have been identified and selective opioid receptor agonists and antagonists have been developed, the aim of the study was to determine the roles of opioid receptor subtypes in modulation of itch/scratching and nociceptive responses in monkeys. Scratching responses were counted by observers blinded to the experimental conditions. Nociceptive responses were measured by a warm water (5^0C) tail-withdrawal assay. Following either intravenous or intrathecal administration of opioid receptor agonists targeting different receptor subtypes, only μ-opioid receptor agonists elicited scratching responses. More importantly, intrathecal administration of the nociceptin/orphanin FQ peptide (NOP) produced profound antinociception in the absence of scratching responses. In addition, systemic administration of kappa opioid receptor agonists attenuated intrathecal morphine-induced scratching and the anti-scratching effects were reversed by pretreatment with kappa opioid receptor antagonists. Taken together, these results suggest that (*i*) central μ-opioid receptors selectively mediate itch/pruritus produced by systemic or intrathecal administration of opioid analgesics, (*ii*) kappa opioid receptor agonists may have the therapeutic potential as antipruritics for attenuating opioid-induced itch while maintaining opioid-induced analgesia, and (*iii*) activation of spinal NOP receptors may be a potential target for development of spinal opioid analgesics without producing side effects such as itch/pruritus in humans.

THE NEW ITCH SECTION IN ACTA DERMATO-VENEREOLOGICA *(OP27)*

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Itching as a multi-factorial symptom is of interest for various medical specialities. Papers about itch may be published in journals with a research or clinical focus such as e.g. dermatology, neuroscience, physiology, internal medicine, allergy. None of these journals have so far offered a separate section on this topic. In September 2006, Acta Dermato-Venereologica launched a new section called "Itch, pruritus and neurodermatology". Two editors cover the experimental and clinical aspects of this challenging topic trying to review and edit all submitted manuscripts professionally. The first-year experiences of editing this new section will be presented out of the editors' and the manager's perspective.

BRAIN NETWORKS OF ITCH AND SCRATCH *(OP28)*

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The central processing of itch has been demonstrated using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) employing blood oxygen level dependent (BOLD) contrast. In these studies, histamine-induced itch coactivates the anterior cingulate and insular cortex, premotor and supplementary motor areas, cerebellum, primary somatosensory cortex and thalamus. A serious limitation is that all of these studies used healthy human subjects. We present a new technique of brain imaging in chronic itch patients using arterial spin labeling (ASL) fMRI, which seems more suitable to assess pruritus-related brain activity than either PET or BOLD fMRI. We will also present new studies assessing the effects of the fundamental behavioral response to itch, scratching, on brain activity. Our preliminary data has already shown scratching deactivates the anterior cingulate cortex in healthy subjects, an area that appears central to the supraspinal processing of pruritus.

HYPER- AND HYPO-SENSITIVITY TO HISTAMINE IN ATOPIC DERMATITIS: THE EFFECT OF TOPICAL ANTI-INFLAMMATORY THERAPIES ON SENSITIZATION *(OP29)*

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We already reported that histamine-induced itch was enormous in the lesional skin of patients with atopic dermatitis though flare- and wheal-size was almost same with healthy persons, suggesting the role of neuronal sensitization in atopic dermatitis. To investigate the effect of topical anti-inflammatory therapies on this phenomenon, we compared histamine-induced skin reactions before and after topical anti-inflammatory therapies in patients with atopic dermatitis (AD) and healthy volunteers. Histamine was applied iontophoretically to the lesional skin of ten patients (AD skin) and the normal skin of ten healthy volunteers (control skin). The area of flare and wheal and the intensity of itch induced by histamine were measured. The application of histamine was done before and after three-day topical treatments with betamethasone-17-valerate (BV), tacrolimus (FK) or petrolatum. In the control skin, no change was observed in any of histamine-induced reactions after any of the treatments. In AD skin, in the meantime, all of flare- and wheal-area and itch intensity were drastically decreased after the three-day treatments with BV and FK, not with petrolatum, even to a lower level compared to the control skin. These results suggest that the patients with AD are basically hypo-sensitive to histamine but that the hypo-sensitivity is masked by inflammation-induced sensitization in their lesional skin.

OVERVIEW: SEROTONERGIC AND OPIATE DRUGS TO TREAT ITCH *(OP30)*

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Paroxetine, a serotonin re-uptake inhibitor has shown antipruritic potency in polycythemia vera, psychogenic and paraneoplastic pruritus in case reports. Cardiac side effects have to be considered in elderly patients. Mirtazapine is a tetracyclic antidepressant with H1-antihistaminic and serotonin-antagonistic effects. It has been used successfully in cholestasis, uraemia and paraneoplastic pruritus. Due to the pathophysiological significance of serotonin in different diseases such as kidney and liver diseases serotonin receptor antagonists (of the 5-HT3 type) such as ondansetron, tropisetron and granisetron were also used to treat pruritus. However, contradictory results

have hampered randomised controlled clinical studies but case reports still appear intermittently. Opioid receptor antagonists like naltrexone have shown good antipruritic effects in different forms of pruritus. Their advantage is oral application and long-lasting, selective μ-opiate receptor blocking in contrast to others like naloxon and nalmefen. Naltrexone has shown good effects in prurigo nodularis, prurigo simplex, lichen amyloidosus and lichen simplex. Opioid receptor antagonists have often been used successfully in controlled studies for cholestatic pruritus but contradictory results were seen in uremic pruritus.

ANTIPRURITIC POTENCY OF SEROTONIN RE-UPTAKE-INHIBITORS: RESULTS OF A PROOF-OF-CONCEPT STUDY *(OP31)*

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Chronic pruritus is difficult to treat and requires the evaluation of new therapeutic modalities. The modern group of antidepressants, the serotonin re-uptake inhibitors (SSRI), were described in single cases and small case series to exhibit significant antipruritic effects. We therefore initiated a two-arm prospective, POC study applying the SSRI paroxetine and fluvoxamine in a total of 72 pruritic patients (27 men, 45 women, 28–88 years, mean 59.2). 49/72 patients (68.0%) experienced a weak (*n*=9), good (*n*=16) or very good (*n*=24) therapeutic effect. Statistical analysis showed no significant difference between both substances efficacy. In patients with pruritus due to atopic dermatitis, lymphoma and carcinoma, best efficacy was observed. Prurigo nodularis healed completely in 14/31 patients and partially in 17/31 patients. Adverse drug effects were observed in 70.8% of patients at the beginning of treatment; 3 patients discontinued the treatment immediately due to side effects. In summary, this POC study suggests SSRI as one new treatment modality of chronic pruritus and prurigo which has to be confirmed in further double-blind studies.

EVALUATION OF ANTIPRURITIC THERAPY IN A LARGE COLLECTIVE OF PRURITIC PATIENTS: RESULTS OF A RETROSPECTIVE STUDY IN 385 PATIENTS *(OP32)*

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The antipruritic potency of currently used symptomatic therapeutic modalities is often not approved in controlled studies but case series only. However, these data were the basis of the new EDF-European and AWMF-German Guideline for chronic pruritus. The aim of this retrospective analysis was to determine the therapeutic outcome of various antipruritic therapies. The basis was the total collective of patients presented to our specialized ambulance for out-patients with chronic pruritus in 2006. 541 patients presented with chronic pruritus of various origin for diagnostic and therapeutic recommendation. 385/541 (71.2%) of these patients could be followed-up and evaluated for therapeutic outcome. According to the German guideline, patients were treated first line with a high dosage of antihistamines. Second line, after diagnosis of the underlying pruritic disease, etiologically adapted treatment was initiated (e.g. gabapentin in neuropathic pruritus). Third line, a symptomatic treatment in combination or as monotherapy was administrated selected from the substances as follows: naltrexone, pregabalin, paroxetine, or cyclosporin A. In total, 250/385 patients (64.9%) responded to some treatment with moderate (*n*=20; 5.2%; 30–49% pruritus reduction), with good (*n*=71; 18.4%; 50–79% pruritus reduction) or very good pruritus reduction (*n*=159; 41.3%; 80–100% pruritus reduction). 135/385 patients (35.1%) showed no (*n*=117, 30.4%) or weak (*n*=18, 4.7%; 5–29% reduction) response. 118/385 patients (30.7%) reported on a significant reduction of pruritus upon a combination of antihistamines (cetirizine, loratadine, allergodil). 30/385 patients (7.8%) were treated successfully with either gabapentin (*n*=24) or pregabalin (*n*=6). In 7/385 patients (1.8%) the serotonin re-uptake inhibitor paroxetine was administrated with success; in 16/385 patients (4.2%) the immunosuppressant cyclosporin A; in 2 patients (0.5%) naltrexone and in 3 (0.8%) aprepitant. 84/385 patients (21.8%) needed a combination of treatment for significant antipruritic effect. In sum, these findings show that a high number of patients with a chronic pruritus can be effectively treated with peripheral or central acting substances. Interestingly, a high dosage of antihistamines reduces chronic pruritus in about half of the patients.

RELEASE OF GROWTH FACTORS IN HUMAN SKIN *(P33)*

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In patients suffering pruritus, enhanced nerve growth factor (NGF) content was identified in psoriatic skin homogenates and blood plasma of atopic dermatitis patients. Here, we sampled NGF and brain-derived neurotrophic factor (BDNF) from human axilla and upper arm skin by intradermal microdialysis. Concentration of growth factors were analyzed by a multiplexed sandwich ELISA and calculated to total protein content/ml sample volume. Inflammatory skin condition was evoked by repetitive shaving of the axilla. The corresponding area of erythema (>5 cm^2 on average) was assessed by laser Doppler imaging and sensitization to heat quantified by a surface thermode (QST). Excitation of skin nociceptors was induced by the perfusion with citric acid pH3 through the microdialysis catheters. The perceived pH-evoked pain was significantly augmented in the axilla sites as compared to the upper arm ($p<0.02$), but no sensitization recorded at the inflamed site ($p>0.1$). At both control skin sites, i.e. the upper arm and non-shaved axilla, the concentration of NGF declined during the 90 min baseline period from about 7.6 to 4.2 fg/mg/ml. Administration of protons caused a significant release of NGF ($p<0.02$) that was more pronounced in the upper arm as compared to the axilla. During baseline condition BDNF concentration was analyzed at both skin sites at 85 fg/mg/ml on average, and low pH perfusion caused a pronounced BDNF release to about 150 fg/mg/ml in the upper arm and 95 fg/mg/ml in the axilla. Compared to both control skin sites administration of protons

evoked in the inflamed tissue almost a twofold increase of NGF (14.5 fg/mg/ml, $p<0.01$) and BDNF (200 fg/mg/ml, $p<0.02$). The enhanced release of growth factors suggests their elevated generation in inflamed skin. Their identification may provide sensitive peripheral markers for nociceptor sensitisation in atopic skin.

PSYCHOSOCIAL ASPECTS OF ITCH – SOMATOFORM PRURITUS *(OP34)*

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In a psychosomatic meaning itch is as well a bodily aspect as also have mental complaints and is mentally inducible (Niemeier et al., 1999). The research on psychological influences is mainly lower than to look after the physiological and immunological aspects. The somatoform itch (Stangier et al., 2003) is a somatoform disorder with pruritus as diagnosed in the DSM-IV or ICD-10 respectively. For psychosomatic aspects a psychological comorbidity of depression, anxieties and personality disorders should be recognized (Gupta et al., 1994). The comorbidity of pruritus and depression reported in a study by Sheehan-Dare et al. (1990) showed a high correlation of pruritus and depression in comparison to healthy controls. 15 of the patient in the pruritus group and only 5 in the healthy controls reached the level of clinically important depression. Studies with experimentally induced itch by histamine showed the psychological factors while placebo have had the same effects as grenz rays (Fjellner et al., 1989) and mental stress induces pruritus (Fjellner & Arnetz, 1985, Fjellner et al., 1985). Psychiatric patients showed a high prevalence of pruritus in a cohort study by Picardi et al. (2000), when showing that 30% have a comorbidity of pruritus. There are only few studies exploring the anatomy of brain functions related to itch. An itch-induced activation of the anterior cingulate cortex, supplementary motor area, premotor area and inferior parietal lobe was thought to differ from the pattern usually seen under pain (Walter et al., 2005).

ITCH AND MENTAL DISTRESS AMONG ADOLESCENTS. PRELIMINARY RESULTS FROM A CROSS-SECTIONAL STUDY *(OP35)*

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Objectives: To study the association between itch and mental distress among late adolescents in non-healthcare seeking population. *Method*: A cross-sectional questionnaire-based study carried out in Oslo, Norway, collecting self-reported data on itch (no itch, a little itch, quite a lot of itch and very much itch), physical and mental health. Mental distress was ascertained by The 10-item Hopkins Symptoms Check List (HSCL-10). *Results*: A total of 3416 adolescents responded. The response rate was 80%. Itch (all grades) was more prevalent among females (33.8%) than among males (24.8%), and also more prevalent among those with non-western origin, low educational background and among cigarette smokers. Prevalence of itch in adolescents with mental distress (n=823) was 47.5%, asthma 44.0%, hay-fever 41.5% and eczema 69.5%. Bivariate analyses gave the following estimated associations with itch: Mental distress 3.5 (2.8; 4.5), females 1.9 (1.5; 2.5), low education level 1.5 (1.2; 2.0), asthma 2.3 (1.5; 3.4), hay-fever 2.4 (1.8; 3.2) and eczema 10.5 (7.8; 14.1). When adjusting for gender, educational level, cigarette smoking and atopy the odds ratio for mental distress was 3.3 (2.5; 4.5). *Conclusion*: This study shows a strong association between itch and mental distress among adolescents in the general population, also when adjusting for socio-demographic factors and asthma, hay-fever and eczema.

THE ROLE OF ATTENTIONAL FOCUS AND INTERPRETATION OF BODILY SENSATIONS ON ITCH SENSITIVITY *(OP36)*

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It is well-known that the perception of sensations can be affected by psychological factors of sensory information processing (van den Bergh et al., 2002). For itch, it has been reported that patients with chronic itch conditions have a lower tolerance for sensory stimuli in general and for itch specifically (van Laarhoven et al., 2007; Ikoma et al., 2004; 2005). This might be due to changes in information processing such as an attentional – or interpretational bias to itch stimuli, including heightened attention and hypervigilance to sensory stimuli or catastrophizing interpretations (van den Bergh et al., 2002; Fortune et al., 2003). In the present study, we examined the possible role of attentional and interpretational bias on sensitivity to itch stimuli in healthy subjects. In an experimental design, different stimuli of Quantitative Sensory Testing (QST) were applied for examining perception thresholds, tolerance thresholds and itch sensitivity. We expected that individuals with a higher attentional focus for somatosensory stimuli would be particularly characterized by lower perception thresholds, while subjects with more catastrophic interpretational bias toward somatosensory stimuli would report lower tolerance thresholds as well as higher itch reports to all kinds of stimuli. Attentional focus was measured with the Body Vigilance Scale (BVS) and interpretation bias was measured with the modified Body Sensation Interpretation Questionnaire (BSIQ-m). Preliminary results generally indicate that both attentional and interpretational bias towards bodily sensations affect itch sensitivity.

THE INFLUENCE OF ITCHING ON ATOPIC DERMATITIS PATIENTS' WELL-BEING *(OP37)*

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Itching is a very frequent symptom of atopic dermatitis (AD). The aim of this study was to evaluate the relationships between pruritus and quality of life, symptoms of depression and experienced stress in adult patients with AD. Eighty-nine adult patients (30 men, 69 women) suffering from AD were included. The study was based on specially designed questionnaire con-

taining demographic and clinical data. The intensity of pruritus was assessed according to a 10-point visual analogue scale and the questionnaire method, quality of life (QoL) according to Dermatology Life Quality Index, and symptoms of depression with Beck's Depression Inventory (BDI). Moreover, stress experienced by patients was evaluated according to Social Readjustment Holmes and Rahe Scale and stress self-assessment scale. The mean intensity of pruritus according to VAS was 7.92±2.16 points, and according to questionnaire was 14.5±5.0 points. The intensity of pruritus correlated with disease severity assessed by SCORAD (VAS: r=0.46, $p<0.001$, questionnaire: r=0.65; $p<0.001$). A strict correlation between pruritus and QoL was found (VAS: r=0.44, $p<0.001$, questionnaire: r=0.49, $p<0.001$) as well as between pruritus and BDI (VAS: r=0.41, $p<0.001$, questionnaire: r=0.51, $p<0.001$). Moreover, patients with symptoms suggesting depression (BDI >10 points) had more intense pruritus compared with the rest of patients (VAS: 9.12±1.58 vs. 7.58±2.19 points, $p<0.001$, questionnaire: 18.4±3.6 vs. 13.4±4.8 points, $p<0.001$). The intensity of pruritus was also related to stress. In conclusions, itching intensity in AD patients plays an important role in determining patients' psychosocial well-being. Patients with AD require an effective, long-term antipruritic therapy to improve their QoL and to reduce the risk of the development of reactive depression.

Poster Abstracts (P1-P29)

ENDOTHELIN-CONVERTING ENZYME-1 DEGRADES SUBSTANCE P IN ENDOSOMES TO REGULATE RESENSITIZATION OF THE NEUROKININ 1 RECEPTOR *(P1)*

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Substance P (SP) is localized in unmyelinated sensory nerve fibers in skin. Release of SP causes redness, wealing and itching. The mechanisms of recycling and resensitization of G protein-coupled receptors (GPCRs) are poorly understood. We demonstrate a new biological process by which an endopeptidase, endothelin-converting enzyme-1 (ECE-1), regulates resensitization of the SP neurokinin 1 receptor (NK_1R). SP and NK_1R traffic to acidified early endosomes, where ECE-1 degrades and inactivates SP to promote dissociation of the NK_1R from β-arrestins. The NK_1R, freed from SP and β-arrestins, quickly recycles and resensitizes. This mechanism also regulates resensitization of receptors for neurokinin B and calcitonin gene-related peptide. We propose that peptidases such as ECE-1 degrade peptides in endosomes to control receptor recycling and the sensitivity of cells to peptide hormones and neurotransmitters. The discovery that ECE-1 regulates recycling and resensitization of GPCRs such as NK_1R establishes a new function of intracellular endopeptidases in the regulation of NK_1R-mediated processes such as inflammation, pain and psychiatric disorders.

ECE-1 REGULATES RECEPTOR RECYCLING-INDEPENDENT RESENSITIZATION *(P2)*

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Substance P (SP) is localized in unmyelinated sensory nerve fibers in skin. Release of SP causes redness, wealing and itching. Phosphorylation of G protein-coupled receptors plays an important role in regulating their function. Endothelin-converting enzyme 1 (ECE-1) inactivates internalized SP within early endosomes thereby accelerating resensitization of these cells. The time course of degradation of internalized SP by ECE-1 is independent from the concentration of the ligand. Confocal laser scanning microscopy shows that intracellular degradation of SP by ECE-1 allowed dissociation of β-arrestin-1 from early endosomes and trafficking of β-arrestin-1 to the cell membrane. Resensitize of NK_1R to a second challenge of SP is not mediated by recycling of the internalized NK_1R but rather by dephosphorylation of cell membrane-located receptors by a fostriecin-senitive protein phosphatase 2A (PP2A). Surface receptor binding assays demonstrate that SP binding sites did not recover 2 h after challenge of cells with SP, a time point where cells are normally fully resensitized. The stimulation with SP induced association of PP2A on cell membrane-located NK_1R. We have thus identified that resensitization of NK1R-expressing cells is mediated by reactivation of cell membrane-associated NK_1R by PP2A.

AGONIST-INDUCED ENDOCYTOSIS OF RAT SOMATOSTATIN RECEPTOR 1 *(P3)*

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Somatostatin-14, is localized in sensory nerve fibers in skin. Release of somatostatin-14 modulates wealing and itching. Somatostatin-receptor 1 (sst1) is an autoreceptor in the central nervous system that regulates the release of somatostatin. Sst1 is present intracellularly and at the cell surface. To investigate sst1 trafficking, rat sst1 tagged with epitope was expressed in rat insulinoma cells 1046-38 (RIN-1046-38) and tracked by antibody labeling. Confocal microscopic analysis revealed colocalization of intracellularly localized rat sst1-HSV with Rab5a-GFP and Rab11a-GFP, indicating the distribution of the receptor in endocytotic and recycling organelles. Somatostatin-14 induced internalization of cell surface receptors and reduction of binding sites on the cell surface. It also stimulated recruitment of intracellular sst1-HSV to the plasma membrane. Confocal analysis of sst1-HSV revealed that the receptor was initially transported

within superficial vesicles. Prolonged stimulation of the cells with the peptide agonist induced intracellular accumulation of somatostatin-14. Since the number of cell surface binding sites did not change during prolonged stimulation, somatostatin-14 was internalized through a dynamic process of continuous endocytosis, recycling and recruitment of intracellularly present sst1-HSV. Accumulated somatostatin-14 bypassed degradation via the endosomal-lysosomal route and was instead rapidly released as intact and biologically active somatostatin-14. Our results show for the first time that sst1 mediates a dynamic process of endocytosis, recycling, and reendocytosis of its cognate ligand.

THE POTENTIAL OF MODERN CHROMATOGRAPHIC-MASS SPECTROMETRIC TECHNIQUES APPLIED TO ITCH MEDIATOR INVESTIGATION *(P4)*

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It is the authors' intention to highlight the applicability of specialized hyphenated mass spectrometric techniques to the analysis of human biofluids and tissue: in particular with regard to the identification of protein and peptide-based mediators regulating itch. The process of nociception involves the body's use of various biomolecules for signalling at both peripheral and central sites. These biomolecules can be sampled by various means and those samples subjected to analysis by the title techniques. The presentation will discuss the methods of sample collection, the treatment of the samples to ensure fitness for purpose, the capabilities of the instrumentation, the translation of data into information and the statistical analysis of data to differentiate sub-populations within the study population.

POSSIBLE INVOLVEMENT OF LIPOXIN A_4 IN ITCH-ASSOCIATED RESPONSE OF MOSQUITO ALLERGY IN MICE *(P5)*

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Mosquito bite causes itching and cutaneous reactions, such as wheal and flare. Mosquito allergy causes scratching in mice, which is inhibited by the 5-lipoxygenase inhibitor zileuton, but not by antagonists of leukotriene B_4 and cysteinyl leukotrienes. In this study, we examined the participation of lipoxin A_4 (LXA_4), one of the 5-lipoxygenase metabolites, in mosquito allergy-associated itch. Male ICR mice were sensitized by injecting intradermally an extract of salivary gland of mosquito (ESGM) into the caudal back twice a week for four weeks. An intradermal injection of ESGM into the rostral back of the sensitized mice induced scratching. This action was inhibited by *N-t*-butoxycarbonyl-methionine-leucine-phenylalanine, a LXA_4 receptor (LXR) antagonist. The concentration of LXA4 in the skin injected with ESGM was increased in the sensitized mice. LXA_4 itself elicited scratching in the sensitized, but not naïve, mice. The number of CD4-positive T cells, which is known to express LXR, and the expression level of LXR in the skin were higher in the sensitized mice than in naïve mice. LXR mRNA was detected by PCR in CD4-positive T cells isolated from the skin of sensitized mice. Adoptive transfer of CD4-positive T cells from the sensitized mouse into the skin of naïve mice induced LXA_4-elicited scratching. The results suggest that LXA_4 and CD4-positive T cells participate in mosquito allergy-associated itch.

ELECTRON MICROSCOPIC STUDY ON SPROUTING OF NERVE FIBERS INTO EPIDERMIS OF DRY SKIN MICE *(P6)*

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We examined electron microscopical feature of the nerve fiber in epidermis of mice with spontaneous itch-associated scratching behavior. The itchy mouse model was prepared by repetitive treatment with acetone/ether and subsequent water on the shaved skin at rostral back for consecutive 6 days (designated as a dry skin mouse). Observation of scratching behaviors of intact mice with shaved skin and dry skin mice was performed by videotaping for 2 h. The number of scratching bouts to the rostral part of back in the dry skin mice (170+32, n=4) was greater than that in intact mice (17+2, n=4). The value of stratum corneum hydration of the treated skin in the dry skin mice (20.1+4.0%) was lower than that in intact mice (35.0+1.1%). Histologically, epidermis of dry skin mice was increased in thickness with marked hyperkeratosis. Immunohistochemistry using antibody to a pan-neuronal marker, protein gene product 9.5 (PGP9.5), demonstrated sprouting of nerve fibers into the epidermis of dry skin mice, while only a few or no PGP9.5 immunoreactive nerve fibers were found in the epidermis of untreated mice. Ultrastructurally, PGP9.5 immunoreactive nerve fibers without obvious association of Schwann cell were found to locate among the epidermal keratinocytes in dry skin mice. These results suggest that unmyelinated C fiber-neurons sprouting into epidermis are related to the development of spontaneous itching caused by skin dryness.

CESSATION OF REPEATED MORPHINE ENHANCE HISTAMINE- AND SEROTONIN-INDUCED SCRATCHING RESPONSES IN MICE *(P7)*

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It is well known that scratching responses is affected under exist of psychological stress in such as atopic dermatitis. On the other hand, morphine is a typical narcotic drug that induce scratching response as adverse drug reaction. Although long term treatment of morphine will induce tolerance and dependence, morphine withdrawal causes psychological and physiological stressful changes in human. Thus, we thought that cessation of repeated morphine may affect the state of itch sensation. In this study, we evaluated the effects of morphine withdrawal on scratching behaviors induced by histamine and serotonin in mice. Morphine with gradually increasing doses was administered every 10 mg/kg per day from 10 to 50 mg/kg i.p., twice daily for 5 consecutive

days. After each withdrawal period, histamine or serotonin was intradermally injected to the rostral part of the back. The number of scratching behavior in 60 min was totaled. As results, 24 h after morphine cessation, histamine- and serotonin-induced scratching behaviors were clearly enhanced. This enhancing effect still remained as tendency at 48 h after cessation, and disappeared at 72 h. Relative adrenal weight showed tendency to increase and relative thymus weight decreased significantly. Moreover, increase of plasma corticosterone levels changed parallel to the number of scratching, and showed statistically significant in 24 h after morphine cessation. However, loading corticosterone to mice did not enhance histamine-induced scratching behavior. Thus, it is suggested that morphine-withdrawal induces stress state and enhances itch sensation, but it may not be caused by increased plasma corticosterone.

INTRACISTERNAL MORPHINE-INDUCED FACIAL SCRATCHING AND ANALGESIA ARE REGULATED DIFFERENT μ-OPIOID RECEPTOR SPLICE VARIANTS IN MICE *(P8)*

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The central action of opioids elicits itch and analgesia probably through mu-opioid receptors (MOR). Currently, more than 20 MOR splice variants that are produced by alternative splicing of the gene encoding MOR (Oprm gene) have been identified in mice. The existence of many variants permits us to speculate that MOR splice variants are involved in different pharmacological actions such as elicitation of itch or inhibition of pain. The present study was conducted to determine the role of MOR splice variants in the regulation of itch and pain by using exon-specific antisense oligodeoxynucleotides (AS-ODN) for Oprm gene. Male ICR mice were given AS-ODN (10 μg/5 μl, i.c.) for exon 1–10 or saline on days 1, 3 and 5. On day 6, morphine (1 nmol/5 μl, i.c.)-induced itch and analgesia were assessed by the counting of facial scratch bouts and tail pressure test, respectively. Morphine-induced facial scratching was inhibited by pretreatment with AS-ODN for exon 4, but not with AS-ODNs for the other exons. Morphine-induced analgesia was inhibited by pretreatment with AS-ODN for exon 9, but not the other exon-specific AS-ODNs. These results suggest that MOR-1 encoded by splice variants containing exon 4 and MOR-1C/MOR-1D encoded by splice variants containing exon 9 are involved in morphine-induced itch and analgesia, respectively.

ANTIPRURITIC EFFECTS OF NALFURAFINE, THE KAPPA OPIOID RECEPTOR AGONIST *(P9)*

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Nalfurafine, a kappa opioid receptor agonist, inhibits scratching behavior induced by chloroquine (CQ, an antimalarial agent), agmatine (an endogenous amine) and 5'-guanidinonaltrindole (GNTI, a kappa opioid receptor antagonist) in mice as well as cholestasis secondary to ethinylestradiol (EE) injections in rats. Male SW mice (20–25 g, *n*=8) and male SD rats (175–200 g, *n*=8) were used. Mice were injected with saline, CQ (1.25–40 mg/kg), agmatine (2.5–160 mg/kg) or GNTI (0.03–3 mg/kg) s.c. behind the neck and the number of hindleg scratches directed to the neck was counted for 30 min. Nalfurafine was administered s.c. in a fixed dose (0.02 mg/kg at –20 min) against CQ and agmatine and in increasing doses (0.001–0.03 mg/kg) against GNTI (0.3 mg/kg). Oral nalfurafine (0.02–0.12 mg/kg at 45 min) inhibited CQ (10 mg/kg)-induced scratching. Furthermore, nalfurafine (0.02 mg/kg) significantly inhibited scratching when it was given 5 min after GNTI (0.3 mg/kg). Tolerance to scratching did not occur when GNTI (0.3 mg/kg) was given once a day for 8 days (391±75 scratches on day 1 and 345±55 on day 8). Also, when mice were injected with nalfurafine (0.02 mg/kg) 20 min before GNTI, once a day for 10 days, tolerance did not develop to the anti-scratch effect (31.7±13 scratches on day 1 and 14.3±6.9 on day 10). Rats were injected with EE (2 mg/kg, s.c.) once a day for 14 days to induce cholestasis. On day 14, the rats received either saline or nalfurafine (0.005–0.02 mg/kg, s.c.) 20 min before EE. Nalfurafine antagonized scratching in a dose-dependent manner. Our results indicate that *a*) the kappa opioid system is involved, at least in part, in the pathogenesis of scratch, *b*) nalfurafine has antipruritic activity against chemically diverse pruritic agents and *c*) nalfurafine may be used to treat cholestatic pruritus.

SIMILAR PATTERNS OF ACTIVITY-DEPENDENT SLOWING OF CONDUCTION VELOCITY IN C FIBERS OF HUMANS AND PIG *(P10)*

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Itch fibers were found among mechano-insensitive (silent) human C-fibers using microneurography. The silent C afferents show a pronounced activity-dependent slowing (ADS) of the conduction velocity (CV). In order to establish an animal model that may reflect conditions in human, we studied axonal properties of C-fibers in anesthetized pigs with electrical stimulation paradigms identical to those used in man. We recorded C-fibers from saphenous nerve using teased fiber technique. Electrical stimuli were used to search for C-fibers in the skin. After electrical identification of a receptive field (RF), 2 needle electrodes were inserted intradermally for repetitive electrical stimulation. Only C-fibers (CV<2 m/s) were analyzed. ADS was assessed for *a*) 20 pulses at 0.125 Hz and 0.25 Hz and 30 pulses at 0.5Hz; *b*) 2 Hz stimulation for 3 min. Then, the RF was tested with von Frey hairs (cut-off 1N) and contact heat stimuli (increase 2°C per 4 s; cut-off 50°C). We recorded 88 C-fibers. Based on ADS and response to natural stimuli, the fibers were classified as: *low threshold (<10 mN) mechano-sensitive* (24% of all fibers): CV 1.4±0.1 m/s; ADS (*a*): 1.8±0.2% (*b*): 11.5±1.2%; heat threshold: 40.7±1.8°C; *high threshold (14–150 mN) mechano-sensitive* (18%): CV 1.05 ± 0.1m/s; ADS (*a*): 2.5 ± 0.3% (*b*): 17.3±1.4%; heat threshold: 44±1.7°C; *mechano-insensitive, silent* (25%): CV 0.9±0.1 m/s; ADS (*a*): 5.6±0.5%, (*b*): 26±1.6%; one was heat responsive (48°C); *sympathetic* (33%): CV 0.8 0.1 m/s; ADS (*a*): 1.6%±0.2% (*b*): 6±0.3%. In conclusion, slowing of the conduction velocity discriminates subgroups of cutaneous C-fibers in pig as it does in humans. Thus, the pig appears to be an appropriate model to investigate axonal properties of C-fibers.

RESPONSES AND MODULATION OF MONKEY SPINOTHALAMIC TRACT NEURONS TO ITCH-PRODUCING AND ITCH-INHIBITING STIMULI *(P11)*

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We used electrophysiological techniques to examine monkey spinothalamic tract (STT) neurons for responses to the itch-producing agents histamine and cowhage. Cowhage consists of the trichomes from the tropical legume *Mucuna pruriens* and produces itch through a non-histaminergic mechanism. One-third of STT neurons examined responded to one of the itch-producing agents, but surprisingly, no cell responded to both histamine and cowhage. The duration of the responses to either pruritogen was similar to the duration of itch produced by either agent when applied to humans. These results suggest that at least two separate populations of STT neurons exist for the transmission of itch information to the brain. The projection targets of pruritogen-responsive STT neurons were determined using antidromic mapping. Both histamine and cowhage types of STT neurons sent axons to the ventral posterior lateral n. as well as to several nuclei within the posterior thalamus. We examined whether the activity of pruritogen-responsive STT neurons could be modulated by stimuli that modulate the perception of itch. Scratching the receptive field of resting STT neurons had an excitatory effect. In contrast, scratching the receptive field during a response to histamine or cowhage transiently reduced the frequency of action potentials. These results suggest that the response properties of STT neurons are state dependent and that the commonly experienced phenomenon of blocking itch with pain may be explained by an inhibitory mechanism at the level of the spinal cord.

LOW PERCENTAGE OF POTENTIAL ITCH-SIGNALING SUPERFICIAL SPINAL NEURONS PROJECT IN SPINOTHALAMIC OR SPINOPARABRACHIAL PATHWAYS IN RAT *(P12)*

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Current evidence indicates that itch and pain are signaled by distinct sub-populations of neurons with input from afferent fibers selectively responsive to pruritic or algesic stimuli. Human pain and itch are transmitted via the spinothalamic tract (STT) but it is unknown if this is true for rodents. We used a double-label strategy to investigate if potential itch-signaling spinal neurons project in the STT or spinoparabrachial (SPB) tracts in rats. Cholera toxin B-subunit (CTB; 100–500 nL) was microinjected into the ventrobasal thalamus or parabrachial nucleus of anesthetized rats. After a 2-day survival, rats were reanesthestized and received intradermal injections (nape of neck contralateral to CTB injection) of 5-HT at a dose (100 µg/5 µl) that elicits maximal hindlimb scratching behavior. Rats were perfused 2 h later and upper cervical spinal cord sections processed in a double-label procedure to stain nuclei expressing fos-like immunoreactivity (FLI) black, and CTB-containing neurons brown. Counts of FLI, retrogradely-labeled STT and STB cell bodies, and double-labeled cells were made under light microscopy. In all animals, FLI was distributed in superficial laminae I-II in the far-lateral aspect of the upper cervical dorsal horn. Retrogradely labeled cells were distributed across lamina I and in deeper locations as previously reported. 1.9% of STT projection cells and 4.5% of SPB cells were double-labeled for nuclear FLI. These results indicate that only a small percentage of superficial dorsal horn neurons activated by pruritic stimulation ascend in these two pathways. Assuming that 5-HT-responsive cells participate in signaling itch, then itch is either signaled by a small subpopulation of ascending projection neurons or is additionally transmitted via another as yet unspecified pathway.

DESCENDING CONTROL OF ITCH SENSATION BY 5-HT NEURONS *(P13)*

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Descending 5-HT neurons play an important role in pain modulation, but their role in transmission of itch signals remains unclear. Our laboratory has previously generated Lmx1b conditional knock-out mice ($Lmx1b^{f/f/p}$), which lack all 5-HT neurons in the central nervous system due to the failure of central 5-HT neurons to survive in the absence of Lmx1b. $Lmx1b^{f/f/p}$ mice preserve an intact peripheral 5-HT system and exhibit normal locomotor activity, and thus provide a unique animal model for studying the role of central 5-HT neurons in itch sensation. We found that the scratching behaviors induced by intradermal injection of compound 48/80 or chloroquine were significantly attenuated in $Lmx1b^{f/f/p}$ mice compared with wild-type mice. Opioid-induced pruritus has been an annoying side effect in pain management, and whether 5-HT neurons are involved in opioid-induced pruritus is unknown. We found that intrathecal morphine-induced scratching behavior was significantly reduced in either $Lmx1b^{f/f/p}$ mice or mice whose 5-HT was depleted from the spinal cord by pretreatment with 5,7-dihydroxytryptamine (5,7-DHT). Taken together, our data suggest that 5-HT neurons play an important role in itch sensation, and descending 5-HT fibers may modulate a balance between pain and itch.

THE ACTIVATION OF BRAIN NETWORKS DURING SCRATCHING *(P14)*

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Neuroimaging studies have examined the neural networks activated by pruritus but not its behavioral response, scratching. In the current study, we examine the central effects of scratching using blood oxygen level dependent fMRI (BOLD fMRI) in 13 healthy human subjects. Subjects underwent functional imaging during scratching of the right lower leg. Scratching stimulus was started 60 sec after initiation of fMRI acquisition and was cycled between 30-sec duration applications of scratching and 30-sec duration applications of no stimuli. Our results show repetitive

scratching induces robust bilateral activation of the secondary somatosenosory cortex, insular cortex, inferior parietal lobe and cerebellum. In addition, we show the same stimulus results in robust deactivation of the anterior and posterior cingulate cortices. This study demonstrates brain areas (motor, sensory and non-sensory) activated and deactivated by repetitive scratching. Future studies that investigate the central effects of scratching in chronic itch conditions will be of high clinical relevance.

INVOLVEMENT OF PROTEINASE-ACTIVATED RECEPTOR-2 IN SPONTANEOUS SCRATCHING OF MICE WITH ATOPY-LIKE DERMATITIS *(P15)*

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Several proteinases have been shown to induce itch in humans. Recently proteinase-activated receptor 2 (PAR_2) has been suggested to be involved in itch of atopic dermatitis detailed mechanisms are unclear. The present study was conducted using NC mice to confirm the involvement of the proteinase-PAR_2 system in itch of chronic dermatitis. When kept long (12–15 weeks) under conventional environment, NC mice showed chronic dermatitis and spontaneous scratching. But NC mice housed under specific pathogen free environment showed no skin lesion and few scratching. The activity of cutaneous tryptase, assayed by using N-*p*-Tosyl-Gly-Pro-Arg *p*-nitroanilide as a substrate, and the expression level of mRNA encoding mast cell proteinase-6 and -7, known as murine tryptase, were increased in the lesional skin of the mice. Pretreatment with the serine proteinase inhibitor nafamostat mesilate (1–10 mg/kg, i.v., –5 min) suppressed both scratching and the tryptase activity in the mice with dermatitis. An intradermal injection of the PAR_2-activating peptide SLIGRL-NH_2 (10–100 nmol/site) dose-dependently elicited scratching in naive NC mice. TFLLR-NH_2 (PAR_1 agonist), SFNGGP-NH_2 (PAR_3 agonist) and AYPGKF-NH_2 (PAR_4 agonist) were without effects. Real-time PCR assay and immunohistochemistry revealed the increased expression of PAR_2 mRNA in the lesional skin of the mice. PAR_2-like immunoreactivity was localized in the keratinocytes in the murine skin. The results suggest that the tryptase-PAR_2 system is involved in spontaneous scratching of NC mice with chronic dermatitis. Tryptase inhibitor and/or PAR_2 antagonist may be effective against itch of atopic dermatitis.

DEVELOPMENT OF ATOPIC DERMATITIS-LIKE SCRATCHING MODEL IN HAIRLESS MICE AND ANALYSES OF ITS PATHOPHYSIOLOGIC MECHANISMS *(P16)*

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To elucidate pathophysiologic mechanisms of itching in atopic dermatitis (AD), we have developed an animal model showing AD-like skin inflammation accompanied with itch-related scratching, and analyzed mechanisms of the symptoms. HR-1 hairless mice fed with a special diet, HR-AD, showed barrier disruption in the skin, and scratching with prolonged duration on and after the day 28 from the start of feeding. In addition, on day 56, inflammatory changes, including increased number of skin cellular infiltrates and elevated levels of serum immunoglobulin E, were observed in HR-AD-fed mice. In contrast, such changes were not seen in mice fed a normal diet at all. The prolonged scratching was ameliorated by treatment with petrolatum ointment, depending on the recovery of skin barrier function. Additionally, extension of nerve fibers into the epidermis was detected in HR-AD-fed mice. These results thus suggest that hypersensitivity to exogenous irritants caused by skin barrier dysfunction and/or nerve fiber extension is involved in the itch-related scratching in this model. Next, to clarify mechanisms underlying the skin barrier dysfunction, effects of supplementing nutrients to HR-AD were investigated. Consequently, deficiency of linoleic acid in HR-AD is responsible for the skin barrier dysfunction. On the other hand, we recently demonstrated that ethanol intake markedly aggravated the scratching response in HR-AD-fed mice, while its mechanism remains to be elucidated. Taken together, this animal model could be used to elucidate pathophysiologic mechanisms of itching in human AD and to develop appropriate drug therapies.

THE BRAIN PROCESSING OF PRURITUS IN ATOPIC DERMATITIS *(P17)*

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Identifying brain networks that underlie itch in chronic pruritic states has not been previously performed. Previous studies have used either blood oxygen level dependent functional MRI (BOLD fMRI) or positron emission tomography (PET) to assess brain activity of histamine-induced itch in healthy volunteers. We present a new technique of fMRI using Arterial Spin Labeling (ASL) that is more suited to assess pruritus-related brain activity due to its ability to capture steady state long-term changes. In the current study, we compared the central processing of pruritus in 8 healthy and 8 atopic dermatitis subjects ASL fMRI. Itch stimulus was evoked by histamine iontophoresis into healthy and lesional skin at the ventral forearm of healthy and atopic dermatitis subjects, respectively. All images were acquired on a 1.5 Tesla GE scanner with a standard pulsed ASL technique, Q2TIPS-FAIR. General linear modeling analysis (FSL) was used to identify regional and global changes in CBF related to itch. The results of the present study show that ASL fMRI is a sensitive technique to detect regional itch-induced changes in cerebral blood flow in atopic dermatitis and healthy subjects during histamine-induced itch. The data also suggests that the brain processing of itch in atopic dermatitis subjects is significantly different than in healthy subjects. Moreover, this is the first study to demonstrate a significant correlation between brain activity in the anterior cingulate cortex (ACC) and both itch intensity and disease severity of atopic dermatitis. The ACC may play an important role in the brain processing of itch. Future studies that assess the brain processing of pruritus in other chronic pruritic conditions and techniques that target the CNS to attenuate pruritus will be of major interest.

INVOLVEMENT OF KERATINOCYTE-DERIVED SEMAPHORIN 3A IN EPIDERMAL INNERVATION OF ATOPIC DERMATITIS *(P18)*

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Cutaneous nerve fibers are present at higher densities in the epidermis of patients with atopic dermatitis (AD). The increase of nerve fibers is partly responsible for the intense itch sensations in atopic skin. It is now generally accepted that keratinocyte-derived NGF is one of the mediators determining skin innervation density. On the other hand, the number of epidermal nerve fibers in AD patients is decreased by phototherapy, but the underlying mechanisms are poorly understood. Interestingly, semaphorin 3A (Sema3A), which is a diffusible molecule important in repulsive axon guidance, inhibits NGF-induced sprouting of sensory afferents in adult mammalian spinal cord. Therefore, Sema3A might be involved in the modulation of epidermal innervation in AD. To address this issue, quantitative RT-PCR and immunohistochemistry were performed on skins from healthy volunteers and AD patients before and after PUVA therapy. Nerve fibers in the skins were also stained with an anti-PGP9.5 antibody, and the number of epidermal nerve fibers was counted. The analyses revealed that both epidermal Sema3A mRNA and protein levels were decreased in AD patients compared with those in healthy volunteers, while the number of epidermal nerve fibers was significantly increased in the AD patients. After PUVA therapy, both epidermal Sema3A mRNA and protein levels were upregulated in the treated group compared with those in the non-treated group. Moreover, epidermal nerve densities were decreased in the treated group, concomitant with a decrease of VAS scores. Thus, the epidermal innervation may be regulated by Sema3A levels in the atopic skin, and not only by neurotrophin levels.

POSSIBLE ROLES OF EPIDERMAL OPIOID SYSTEMS IN PRURITUS OF ATOPIC DERMATITIS *(P19)*

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The μ-opioid (β-endorphin/μ-opioid receptor) and κ-opioid (dynorphin A/κ-opioid receptor) systems play pivotal roles in the modulation of pruritus in the central nervous system. The μ-opioid system has also been identified in human epidermis, raising the possibility that the system controls the peripheral itch. However, the precise distribution of the κ-opioid system has not yet been clarified in human epidermis. To address this issue, RT-PCR and immunohistochemical analyses were performed on cultured keratinocytes and normal skins from humans. The analyses revealed that epidermal keratinocytes express κ-opioid receptor and its ligands, dynorphin A (1–17) and (1–8). Moreover, expression for μ- and κ-opioid systems was examined immunohistochemically in skin biopsies from healthy volunteers and patients with atopic dermatitis (AD) before and after PUVA therapy. Our expression analyses showed that only the κ-opioid system, not the μ-opioid system, was downregulated in the epidermis of AD patients. The downregulation of the μ-opioid system and the restoration of the κ-opioid system by PUVA therapy were observed in the AD patients, concomitant with a decrease of VAS scores. These results suggest epidermal opioid systems are associated with the modulation of pruritus in AD. This new finding may help us to understand the control mechanism of peripheral itch.

CLINICAL CHARACTERISTICS OF ITCHING IN ADULT PATIENTS SUFFERING FROM ATOPIC DERMATITIS *(P20)*

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Itching belongs to one of four main criteria of atopic dermatitis (AD). The aim of this study was to evaluate the clinical manifestation of itching among adult patients with AD. Eighty-nine adult patients (30 men, 69 women) suffering from AD were included. The study was based on specially designed questionnaire containing demographic and clinical data. The intensity of pruritus was assessed according to 10-points visual analogue scale and the questionnaire method. At the time of examination 68.5% patients had taken antihistaminic drugs. The mean intensity of pruritus according to VAS was 7.9±2.2 points, and according to questionnaire 14.5±5.0 points. The intensity of pruritus correlated with AD severity assessed by SCORAD (VAS: 0.46, $p<0.001$, questionnaire: r=0.65; $p<0.001$). Positive correlation between age and intensity of pruritus was also observed (VAS: r=0.18, $p=0.09$, questionnaire: r=0.3, $p<0.01$). The most intensive itching was noted in the evening in 47 (52.8%), at night in 34 (38.2%) and in the morning in 10 (11.2%) patients. Thirteen (14.6%) participants declared that the intensity of pruritus did not significantly change during the whole day. Difficulties in falling asleep due to pruritus were mentioned by 80.9% individuals and the necessity of sleeping medication intake was observed in 31.5% patients. Only 11.2% of subjects experienced periods of time without pruritus longer than one month. The intensity of pruritus was increased by dry skin (89.9%), sweat (87.6%), physical effort (65.0%), diet (57.3%) and hot bath (55.1%). The most often used treatment modalities to relief pruritus were emollients (80.9%), antihistaminic drugs (77.5%), topical corticosteroids (68.5%), cold air (37.1%) or water (23.6%) and taking a rest (20.2%). Patients with AD require an effective, long-term antipruritic therapy.

NERVE FIBER DISTRIBUTION IN LICHEN AMYLOIDOSIS *(P21)*

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Lichen amyloidosis is a severe, localized chronic pruritic skin disorder characterized histopathologically by amyloid deposition in the skin without evidence of visceral involvement. Its histopathologic changes are limited to the epidermis and papillary dermis. Although lichen amyloidosis is common in ethnic populations, Hispanic, Asian and African Americans, there is no

data on nerve fiber distribution and nerve fiber anatomy in this severe pruritic disorder. The aim of this study was to determine the nerve fiber distribution as the possible cause of pruritus in lichen amyloidosis. A study of 30 Hispanic patients with clinical and biopsy-proven lichen amyloidosis was compared to 30 healthy Hispanic subjects matched for gender, age and site. Nerve fiber distribution using PGP9.5 stain demonstrated a significant decrease in nerve fibers in the epidermis and dermal epidermal junction but not in dermis in lichen amyloidosis patients. These results may indicate damage to the nerve fibers in this chronic pruritic condition.

SMALL FIBER-NEUROPATHY AS POSSIBLE CAUSE FOR CHRONIC PRURITUS *(P22)*

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Chronic pruritus can be based on very complex neural mechanisms e.g. peripheral or central sensitization. However, another mechanism might be the degeneration of small "nociceptive" fibers. We report on a 55-year-old patient, who was involved in an industrial accident with pelvic burst and damage of the lumbosacral plexus. Subsequently, a chronic pain syndrome developed despite high-dose analgetic medication. This was followed by trophic and vascular disturbances with damage of cutaneous sensory nerve fibers. Clinically, the patient developed a severe attack-like pruritus overlapped with stinging and burning on both legs. The pruritus had a subjective intensity of VAS 8–10. Scratching lesions, i.e. prurigo nodules, were present on the lower legs. The intraepidermal nerve fiber density showed a significant reduction of the unmyelinated C-fibers (stained with PGP9.5) in pruritic skin in comparison to non-pruritic skin. Quantitative sensory testing of the involved skin resulted in pathological values for painful cold, heat and pressure perceptions. The therapeutic interventions by means of oral gabapentin and paroxetine and a topical therapy with capsaicin led to a significant reduction of pruritus and paresthesia about 70%. In small fiber neuropathy, cutaneous unmyelinated C-fibers and small myelinated A delta-fibers exhibit morphological and functional disturbances. Many systemic diseases (e.g. lupus erythematodes) as well as metabolic or toxic disturbances can induce this disease. A close interdisciplinary co-operation as well as the establishment of new diagnostic procedures are necessary for proper diagnostic.

CLINICAL EVALUATION OF A LARGE COLLECTIVE OF PATIENTS WITH CHRONIC PRURITUS: SUBGROUPS, UNDERLYING DISEASES AND CO-FACTORS *(P23)*

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Chronic pruritus is a symptom of many diseases with up to date pending studies investigating prevalence or incidence. This study aimed to describe characteristics of underlying diseases in a large collective of patients. Following parameters were collected from patients presenting in a 3-year period: gender, age, history, skin lesions, laboratory, histological, and radiological investigation. 263 patients (110 men, 153 women; 8 to 95 years; mean 55.9) were included. In 41.8% an underlying dermatosis, in 13.3% a systemic disease including yet unidentified neoplasms and in 0.4% a neurological disorder was found. In 44.5% of the patients, no disease was determined. Among the latter patients, 55.6% mainly elderly patients had accumulation of many co-factors (mainly metabolic-endocrine, haematological disturbances) without clear time- and history-related association between pruritus and underlying disease but finally leading to pruritus. This suggests an own subgroup of patients suffering from "multifactorial" origin of pruritus. The distribution and type of secondary scratch lesions allows no conclusion to the underlying disease. In conclusion, patients with chronic pruritus present an inhomogeneous collective with different underlying diseases including malignancy necessitating through investigation.

PITFALLS OF DIAGNOSING AND TREATING ITCH *(P24)*

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Itching is a distressing symptom that needs precise history, clinical examination and laboratory as well as radiological diagnostics. The interpretation of findings may sometimes be difficult as well as rating the significance when facing various pathological findings in a patient at a time. This is especially challenging in elderly multimorbid patients. Causal and symptomatic aetiologically-orientated therapy need to be frequently combined. Challenges of diagnostics and treatments will be presented on the basis of single case reports.

NEGATIVE INFLUENCE OF ITCHING ON PSORIATIC PATIENTS' WELL-BEING *(P25)*

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The aim of the study was to evaluate the influence of itching on the well-being of patients with psoriasis. A total of 102 patients suffering from psoriasis (mean age 45.2±17.2 years) were recruited. All patients underwent careful dermatological examination. Pruritus intensity was examined by 10-point visual analogue scale (VAS) and the specially designed Questionnaire. The following psychosocial parameters were also evaluated: quality of life (QoL), stigmatization, depressive symptoms and stress. QoL was assessed by the Dermatology Life Quality Index, stigmatization level by the Ginsburg's Stigmatization Questionnaire and 6-Item Scale proposed by Evers group. Depressive symptoms were scored by Beck's Depression Inventory (BDI) and stress according to Holmes and Rahe Scale as well as by the Stress Self-assessment Scale. Ninety-one (89.2%) patients experienced pruritus during psoriasis exacerbation. There was no correlation between disease severity assessed by PASI scale and pruritus intensity. Pruritus intensity significantly correlated with patients' QoL (VAS: r=0.46, $p<0.001$, questionnaire: r=0.38, $p<0.001$), stigmatization level (VAS and Stigmatization Questionnaire: r=0.19, $p=0.06$, VAS and 6-Item Scale: r=0.24, $p=0.02$, Questionnaire and Stigmatization Questionnaire: r=0.36, $p<0.001$, Questionnaire and 6-Item Scale: r=0.33, p=0.001), depressive symptoms (VAS: r=0.23, $p=0.02$,

Questionnaire: r=0.35, $p<0.001$), and stress severity (VAS and Holmes&Rahe Scale: r=0.31, $p<0.01$, VAS and self-assessment scale: r=0.26, $p<0.01$, questionnaire and Holmes&Rahe scale: r=0.17, $p=0.09$, questionnaire and self-assessment scale: r=0.29, $p<0.01$). Pruritus has a big negative influence on the psychosocial status of patients with psoriasis. The presented study clearly indicated the necessity of effective anti-pruritic treatment among psoriatic subjects to improve their well-being.

ACNE ITCH: IS IT A REAL PROBLEM FOR PATIENT WITH ACNE? *(P26)*

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Itching is defined as an unpleasant sensation which leads to a desire of scratching. Scratching of acne lesions is commonly observed among acne patients. The aim of this study was to evaluate the frequency and intensity of pruritus among teenagers suffering from acne. The study was based on specially designed questionnaire containing demographic and clinical data. The intensity of pruritus was assessed according to visual analogue scale. 108 teenagers with acne (49.1% boys and 50.9% girls) were included. The age of patients was 15.8±1.8 years and the positive family history of acne was documented in 65.7% individuals. Pruritus within acne lesions was noted in half (54 subjects) of the patients. Pruritus intensity at the time of examination was 30.9±19.2 points and maximal itching severity whenever in the past accounted 39.5±24.9 points. The intensity of itching was not influenced by age, gender, place of living and acne severity. Patients with a negative family history of acne reported significantly more intense pruritus compared to patients with positive family history of acne (at examination 43.7±14.1 vs. 21.2±17.2, respectively, $p=0.02$, maximal itching: 56.3±22.1 vs. 31.6±22.4, respectively, $p<0.001$). Itching episodes in acne patients lasted mostly short (<1 min– 51.9%, till 10 min – 38.9%) and were relatively seldom (several times a week – 24.5%, at least once a month – 30.2%, less than once a month – 37.7%). However, 31.5% patients declared, that they had used medical treatment to reduce pruritus of acne lesions. Factors aggravating itching were sweat (61.1% of patients), stress (33.3%), physical effort (31.5%), heat (27.8%), fatigue (20.4%) and dry air (16.7%). Factors relieving itching were cold water (20.4%), hot water (16.7%) and cold (16.7%). Itching of mild to moderate severity seems to be a common concomitant symptom of acne lesions.

THE ROLE OF INFLAMMATION AND HEPATITIS VIRUS INFECTION IN UREMIC PRURITUS *(P27)*

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Objectives: Uremic pruritus is still impairing quality of life of hemodialysis (HD) patients mainly because there are limited understanding of its pathophysiology. Chronic inflammation had been suggested to be related to pruritus in some small sample size studies, but no study investigated the relationship between C-reactive protein level (CRP) and severity of pruritus in larger population of HD patients. *Methods*: Patients who had received HD in our unit >3 months participated this study. Patients with mental illness, primary skin disorder or liver cirrhosis were excluded. Visual Analogue Scale (VAS) reported from 0 to 10 and a questionnaire comprised of four questions concerning the pruritus frequency, distribution, scratch severity and effect on sleep were used to evaluate pruritus. *Results*: 340 patients joined this study. The mean age was 59.8 years, 51.5% were male and 44.3% were diabetic. 14.1% had HBV infection and 11.2% had HCV. The average year on dialysis was 3.89 years and average serum hsCRP was 0.59 mg/dl. 37.4% patients had no pruritis at all, while 23.7% had mild pruritus (VAS 1–3), 24.3% had moderate pruritus (VAS 4-7), and 14.6% had severe pruritus (VAS 8–10). The VAS score was positively correlated with all four questions and total score of the questionnaire. By age- and sex-adjusted multivariate analyses, level of hsCRP, presence of hyperphosphatemia, hepatitis B and C virus infection had significant independent association with VAS score. *Conclusion*: Pruritus is still common within HD patients. Higher CRP and hepatitis B or C virus infection are associated with more severe pruritus. Further study on the interplay between contributing factors for inflammation should help to find optimal treatment for uremic pruritus.

SUPPLEMENTATION OF DIAMINE-OXIDASE – A NEW APPROACH IN THE TREATMENT OF HISTAMINE INTOLERANCE *(P28)*

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Histamine is one of the most important messengers for adverse reactions to food, either IgE-mediated or non immune-mediated. Incidence of histamine intolerance (HIT) in the general population is estimated at around 1%. The most common symptoms reported by patients suffering from HIT after ingestion of histamine-rich foods such as red wine, aged cheese, fermented sausages or fish are itching, skin rashes, fatigue, nausea, bellyache, abdominal cramping, diarrhea and dizziness. HIT may be caused by an elevated uptake of histamine in meals, gastrointestinal disorders, the presence of other biogenie amines in food or decreased capability of degrading of histamine. Most HIT-patients show low diamine-oxidase (DAO)-activity in serum (<10 U/ml). The usual treatment of HIT is oral or parenteral antihistaminic medication. A food supplement containing natural DAO derived from pig kidneys has been available in Germany and Austria since 2006. The enzyme is encapsulated in acid-resistant pellets that are packed in standard gelatine capsules (PelLindTM). This formulation ensures the release of highly active enzyme in the small intestine where it supports the degradation of histamine. A pilot study ($n=20$) showed a significant improvement of symptoms in individuals suffering from HIT measured by a score. 1 capsule PelLind™ per meal reduced the intensity of itching at a rate of 70%, the number of skin rashes at a percentage of 65, the occurence of abdominal pain at a rate of 60%, of abdominal spasms at a rate of 80% and the number of cases of diarrhea at a rate of 50%. There was no control group in this observation study. Compared to antihistaminic medication, DAO supplementation provides 2 advantages: the lack of side effects and the prevention of symptoms instead of treating symptoms that have already occurred. For the first time, PelLind™ supports histamine degradation by using a biologically active enzyme of natural origin.

PSYCHOLOGICAL ASPECTS OF ITCH: QUALITATIVE RESEARCH ON OLDER ADULTS LIVING WITH ATOPIC DERMATITIS SINCE CHILDHOOD *(P30)*

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Psychological aspects of the itch-scratch cycle were identified in a qualitative study on the development of expertise in self-management of atopy. The purpose of this dissertation research was to identify the knowledge, skills, and abilities needed and the resources used in self-management of atopy. Six adults aged 45–60 with early-onset atopic dermatitis (AD), asthma, allergic rhinitis, and/or anaphylaxis participated in two semi-structured two-hour interviews, using grounded theory and narrative methodologies. Interviewed participants had severe or moderate AD and allergies, and mostly mild asthma. Previously gathered archival data from 225 eczema patients in an Internet listserv peer support group were used to triangulate the interview data. Participants were asked how they learned to manage their conditions, starting in childhood when symptoms first occurred, through adulthood to their current age. Knowledge, skills, and abilities needed to manage itch were inter-related with the management of other symptoms of atopy. Psycho-physiological experiences of stress that contributed to the itch-scratch cycle and its level of severity included: anxiety, frustration, anger, hopelessness, conflicts between competing cognitive-behavioral demands, and pressure to take action in ambiguous circumstances. Habitual behavioral patterns and situationally-derived cues or triggers also increased the likelihood that psycho-physiological sensations would be interpreted as itch. Different knowledge, skills, and abilities were needed to cope with different types of perceived itch, e.g. scratching that triggers more intense itch vs. scratch that relieves itch, emotional triggers of itch, and itch induced by environmental conditions or contact with allergens. Findings suggest new directions for research.

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