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7th World Congress on Itch (WCI) 2013

September 21–23, 2013 at the Seaport Hotel and World Trade Center, Boston, Massachusetts, USA

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SATURDAY, SEPTEMBER 21, 2013

14:00–16:30 IFSI Board Meeting

15:00–17:00 Congress Registration

17:00–17:15 Greeting and Introduction
Ethan Lerner, Boston and Jacek C. Szepietowski, Wroclaw

17:15–18:45 Distinguished Plenary Lectures
Chairpersons: Yasushui Kuraishi, Toyoma, Jeffrey Bernhard, Worchester, & Jacek C. Szepietowski, Wroclaw
17:15–18:00 **Bernhard Distinguished Lecture**: The YosipovITCH Journey: From Bedside to Basic Science, *Gil Yosipovitch, Philadelphia* (IL01)
18:00–18:45 **Kuraishi Distinguished Lecture**: Is Itch a Specific Sensation? *Earl Carstens, Davis* (IL02)
18:45–20:00 **Welcome Reception**

SUNDAY, SEPTEMBER 22, 2013

07:30–08:00 **Continental Breakfast**

PLENARY SESSION I
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08:00–08:05 Introduction, *Elke Weisshaar, Heidelberg* (IL03)
08:05–08:15 The 5D questionnaire, *Marlyn Mayo, Dallas* (IL04)
08:15–08:25 Aquagenic itch module, *Sonja Ständer, Münster* (IL05)
08:25–08:35 Pitfalls in qualitative aspects of itch questionnaires, *Jörg Kupfer, Giessen* (IL06)
08:35–09:00 Discussion and comments

09:00–09:30 **Launch of a New SIG: Uremic Itch**
Moderators: Thomas Mettang & Jacek C. Szepietowski
09:00–09:15 Uremic pruritus: clinical presentation of the problem, *Jacek C. Szepietowski, Wroclaw* (IL07)
09:15–09:30 Uremic pruritus: establishment of a new SIG, *Thomas Mettang, Weisbaden* (IL08)

09:30–09:45 **Coffee Break**

09:45–10:30 **Special Lecture: Silencing Pain and Itch,** *Clifford Woolf, Boston* (IL09)

10:30–12:00 **Receptors, Channels and Neural Pathways of Itch**
Moderators: Diana Bautista, Xinzhong Dong & Martin Schmelz
10:30–10:50 Neuronal triggering of itch via the atopic dermatitis cytokine TSLP, *Diana Bautista, Berkeley* (IL10)
10:50–11:10 The role of Mrgprs in itch, *Xinzhong Dong, Baltimore* (IL11)
11:10–11:30 Nppb a neuropeptide essential for itch, *Mark Hoon, Bethesda* (IL12)
11:30–11:50 Specific itch pathways: holy grail for clinical pruritus? *Martin Schmelz, Erlangen* (IL13)

12:00–13:00 **Lunch and Poster Session I**

BREAKOUT SESSION I (move freely between tracks)

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13:00–13:20 Spinal dynorphin modulates itch, *Sarah Ross, Pittsburgh* (IL14)
13:20–13:40 VGLUT2-regulated itch – primary afferents and beyond, *Malin Lagerström, Uppsala* (IL15)
13:40–14:00 A semaphorin story in atopic dermatitis, *Kenji Takamori, Tokyo* (IL16)
14:00–14:10 Spinal interneurons mediate the inhibition of itch by counter-stimuli, *Junichi Hachisuka, Pittsburgh* (FC01)
14:10–14:20 Ciguatoxin-induced release of neuropeptides in a sensory neuron-keratinocyte coculture model, *Raphaele Le Garrec, Brest* (FC02)
14:20–14:30 Enigmatic aspects of 5'-GNTI-induced compulsive scratching in mice, *Alan Cowan, Philadelphia* (FC03)

13:00–14:30 Clinical Research Track: Burden of Itch
Moderators: Suephy Chen & Florence Dalgard
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13:40–13:50 Association of primary localized amyloidosis with atopic dermatitis, *Hong Liang Tey, Singapore* (FC04)
13:50–14:00 Influence of scratch lesions and pruritus localization on psychic symptoms, *Astrid Stumpf, Münster* (FC05)
14:00–14:10 Needs of hemodialysis patients suffering from chronic itch: results from patient interviews, *Melanie Weiss, Heidelberg* (FC06)
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15:40–15:50 Toll-like receptor 4 contributes to dry skin-induced chronic itch but not acute itch in mice, *Tong Liu, Durham* (FC09)
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15:00–15:10 Cutaneous T-cell lymphoma and pruritus: The role of IL-31 in the skin, *Leigh Nattkember, Philadelphia* (FC12)
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08:30–08:45 Modeling atopic itch and skin lesions in dogs: allergen challenges in hypersensitive dogs offer optimal translation potential, *Thierry Olivry, Raleigh* (IL23)

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09:10–09:20 Pharmacological characterization of a surgically induced mouse model of cholestatic pruritus, *Tsugunobu Andoh, Toyama* (FC18)

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Paraneoplastic itch, *Ben Zylicz, Basel* (IL24)

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09:10–09:20 Prurigo nodularis: Introduction of a re-defined classification and prurigo activity score (PAS), *Fiona Schedel, Münster* (IL27)

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11:50–12:00 Unequal burden of diseases, unequal participation in clinical trials: Bisexual members in Chittagong district of Bangladesh, *Ariful Haque Mollik, Dhaka* (FC26)

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13:20–13:30 Neuroimaging and behavioural evidence for insular-mediated sharing of affect as the mechanism underlying contagious itch, *Henning Holle, Hull* (FC28)

13:30–13:40 Gene and protein expression of opioid receptors in the skin of psoriasis patients with and without pruritus, *Piotr Kupczyk, Wroclaw* (FC29)

13:40–13:50 Functional connectivity during the cerebral processing of experimental itch compared to pain, *Hermann Handwerker, Erlangen* (FC30)

13:50–14:00 The ion channel TRPA1 is required for chronic itch, *Sarah Wilson, Berkeley* (FC31)

14:00–14:10 Brain circuitry supporting nocebo itch perception in atopic dermatitis, *Vitaly Napadow, Boston* (FC32)

14:10–14:20 Neural recruitment and activity is integral to the pathogenesis of atopic dermatitis, *Sarina Elmariah, Boston* (FC33)

14:20–14:30 Questions and Discussion

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102: Reduced intraepidermal nerve fibre density in prurigo nodularis of different stages, *Svetlana Bobko, Nani Osada, Claudia Zeidler, Andrey Lvov, Sonja Stände*r

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ABSTRACTS: Invited Lectures (IL01–IL32)

BERNHARD DISTINGUISHED LECTURE

IL01

YOSIPOVITCH JOURNEY FROM BEDSIDE TO BENCH

Gil Yosipovitch

Department of Dermatology and Center for Study of Itch, Temple School of Medicine, Philadelphia, USA

In the past two decades, the volume of research on itch neurobiology has grown immensely, However, there is still a significant lack of understanding of the pathogenesis and management of chronic itch. As a resident in medicine I was intrigued with the suffering of dialysis patients with chronic itch and the limited knowledge on this incapacitating symptom. This led me to complete a residency in dermatology and to study the clinical characteristics of chronic itch of different types and developing questionnaires to better understand the unique features of itch. During this time I was introduced to the fascinating field of itch and scratch. I found that there is significant crosstalk between keratinocytes, skin nerves, and the brain. I also learned about differences in itch characteristics in skin and systemic diseases in various ethnic backgrounds. The terrain that my research covers includes exploring the cognitive, emotional and behavioral components of itch and scratching and therapies that can attenuate the itch response. This lecture will cover the collaborative studies I have performed in 3 continents and underlies my continued interest in scratching for an explanation for this common problem.

KURAISHI DISTINGUISHED LECTURE

IL02

IS ITCH A SPECIFIC SENSATION?

Earl Carstens

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A 1971 paper entitled "Is pain a specific sensation?", by Edward Perl, presented an affirmative argument based on then-new discoveries of cutaneous nociceptors and nociceptive-specific central neurons. Similar arguments are presented for itch. Itch and pain are distinct sensations with separate behavioral responses under differential μ-opioid modulation. Nevertheless, pruritogen-sensitive neurons also respond to noxious stimuli. Histamine activates mechanically-insensitive peripheral C-fibers. Other recently-discovered molecular receptors respond to non-histaminergic mediators including cowhage and proteases (via protease-activated receptors [PARs]) or chloroquine (via Mas-related G-protein coupled receptor A3 [MrgprA3]), some expressed by mechanoheat sensitive C- and A-fibers. Most pruritogen-sensitive central neurons also respond to noxious stimuli. We propose that they signal itch, while pain is signaled by a larger population of nociceptive, pruritogen-insensitive neurons. The neuropeptides natriuretic polypeptide B and gastrin releasing peptide may selectively signal itch, along with substance P and glutamate that signal itch and pain. Importantly, capsaicin, which normally elicits nocifensive behavior, instead elicited itch-related scratching in mice in whom the capsaicin receptor (TRPV1) was selectively expressed in MrgprA3-expressing pruriceptors. This supports the argument that pruriceptors are linked to an itch-specific pathway, regardless of whether they are activated by pruritogens or algogens. Perceptual masking may help to discriminate pain from itch.

SIG: QUESTIONNAIRES

IL03

SPECIAL INTEREST GROUP (SIG) QUESTIONNAIRES

[1]Elke Weisshaar, [2]Gil Yosipovitch

[1]Dept. of Clinical Social Med, Occup. and Environmental Dermatol, University of Heidelberg, Germany, [2]Department of Dermatology and Center for Study of Itch, Temple School of Medicine, Philadelphia, USA

Chronic itch affects millions of patients worldwide. It has significant impact on the quality of life of those affected. Tools like questionnaires are needed to better assess the different dimensions of chronic itch. Despite itch being a common complaint, there are few studies describing the use of structured questionnaires. However, the assessment of itch and its associated affects are a significant component of daily clinical practice in itch management. The special interest group (SIG) on questionnaires of the International Society of the Study of Itch (IFSI) has recently published a first consensus paper addressing what domains and structures in itch questionnaires need to be implemented to better assess chronic itch and guide therapy. New works on assessments of different types of itch and future directions are presented.

IL04

THE 5D QUESTIONNAIRE

Marlyn Mayo

Dallas, USA

No abstract provided.

IL05

AQUAGENIC PRURITUS QUESTIONNAIRE (AP-Q): DEVELOPMENT OF A NEW QUESTIONNAIRE TO ASSESS AQUAGENIC PRURITUS

[1]Ulla Koch, [2]Jens Hinrichs, [3]Nani Osada, [2]Linda Dieckmann, [4]Christine Blome, [4]Matthias Augustin, [1]Sonja Ständer

[1]Competence Center Chronic Pruritus, Department of Dermatology, [2]Department of Psychosomatics and Psychotherapy, [3]Institute for Medical Informatics and Biomathematics, all at University Hospital Münster, [4]Center for Dermatological Research (CeDeF), Health Economics and QoL Research Group, German Center for Health Services Research in Dermatology (CVderm), University Clinics of Hamburg, Germany

Aquagenic pruritus (AP) can be found in 16.8% of chronic pruritus patients; however, there is no structured and comprehensive questionnaire that helps to determine precisely the underlying disease. In order to develop an AP questionnaire (AP-Q), patients with AP were interviewed. Based on this, AP-Q was developed and modified according to the results of feasibility analysis and after expert discussions. Over a period of two years, four different versions of the questionnaire were distributed among a

total of 110 patients (61 women; mean age: 54.6± 16.0 years). Statistical analysis revealed three sub-groups of AP patients, namely, patients with a hematological disease (group 1), those with sorbitol intolerance (group 2) and those with AP of unclear origin (group 3). Significant differences in seven items among the groups were noted, such as age, type of water triggering AP, and duration and quality of AP. A short version of the AP-Q was developed on the basis of analysis of results, and should enable diagnosis of the underlying disease in AP in routine medical care. The modified long version of AP-Q permits a comprehensive and structured assessment of AP in the context of clinical trials. Both questionnaires need to be validated in further studies.

IL06

PITFALLS IN QUALITATIVE ASPECTS OF ITCH QUESTIONNAIRES

[1]Joerg Kupfer, [1]Christina Schut, [2]Uwe Gieler

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In recent years, some efforts have been made to improve and to harmonize the measurement of a core set of items for evaluating itch. The importance of various areas (e.g. intensity, duration, course of itch, emotions, influencing factors, Quality of Life) was also investigated in a recent study. In addition, there are now specific recommendations for verbalization of the extreme values of visual analogue scales for measuring the intensity of itch and sleep disturbance. Apparently, however, the specific formulation of the questions to measure these parameters is not yet unified. Resulting problems of comparability of study results will be presented and discussed. Another aspect: Usual steps in the development of questionnaires (study of objectivity, reliability, validity, feasibility, usefulness, economic feasibility, sensitivity to change) were only partially implemented in studies which develop new itch questionnaires. Strengths and weaknesses of currently existing questionnaires are exemplified. In particular, further harmonization and improvement of the measurement of parameters for the characterization of itch seems desirable. Possible first approaches, such as the use of the DELPHI-method and the inclusion of focus groups will be presented.

LAUNCH OF NEW SIG: UREMIC ITCH

IL07

URAEMIC PRURITUS: CLINICAL PRESENTATION OF THE PROBLEM

[1]Jacek C. Szepietowski, [2]Thomas Mettang

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Uraemic pruritus seems to be still an important problem for both patients and doctors. The prevalence of uraemic pruritus varies between the studies and is assessed as 20 to even 80% of dialysis patients. Recent results suggest that the incidence in adult dialysis population is between 30 and 40%. The data on the frequency of this symptom in pediatric chronic kidney disease population are very limited suggesting that about 20% of children from this group are affected by itch. The severity of uraemic pruritus is difficult to be assessed due to different measures used by various research groups. Regardless, uraemic pruritus is a very bothersome symptom significantly decreasing patients' well being and quality of life. It was also documented that uraemic pruritus is associated with increased mortality risk. The etiology of uraemic itch is complex and remains still not fully elucidated. As the etiopathogenesis is not fully understood there is no one treatment of choice available. Several therapeutic algorithms have been proposed, including emollients, ultraviolet B irradiation, gabapentin/pregabalin, nalfurafine, paroxetine or mirtazapine. Uraemic pruritus is a fascinating field, unfortunately still with numerous unanswered questions.

IL08

URAEMIC PRURITUS - ESTABLISHMENT OF A SIG

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[1]German Clinic for Diagnostics, Department of Nephrology, Wiesbaden, Germany [2]Department of Dermatology, Venereology and Allergology, Wroclaw Medical University, Wroclaw, Poland

Pruritus in renal diseases is still an unresolved clinical problem with a significantly negative impact on patients' quality of life. In spite of many patients suffering from pruritus scientific findings of the underlying pathogenesis and therapy are still scarce. As could be shown uraemic pruritus (UP) is underestimated as a major contributor to patients suffering. Against this background a concerted action of dedicated scientists and clinicians focussing on the pathophysiology and therapeutic options is desirable with the goal to further enlighten the problem of UP. Especially new information in basic science on chronic kidney disease could be implemented in the pathophysiological approach to UP. The impact on quality of life, i.e. on well-being, depression and sleep-quality could further be elucidated. A UP-working group could be a platform for discussion of all aspects of pruritus in chronic kidney disease where ideas could be shared, projects could be planned. The working group we propose may act as an informal group of clinicians and scientists interested in the field of pruritus and communication should ideally be web-based. All our activities should not be influenced by the particular interest of a company.

SPECIAL LECTURE: SILENCING PAIN AND ITCH

IL09

SILENCING PAIN AND ITCH

Clifford J. Woolf

Boston Children's Hospital, Boston, USA

The peripheral terminals of primary sensory neurons detect noxious stimuli and pruritogens through molecularly distinct transduction mechanisms. It remains unclear, however, whether the different kinds of pruritogens and mechanical chemical and thermal noxious stimuli activate the same or different afferent fibers. We have utilized a strategy of reversibly silencing specific subsets of pruritogen- and noxious stimulus-sensitive sensory axons by targeted delivery of a charged sodium-channel blocker through large pore ion channels. We find that functional blockade of histamine itch did not affect the itch evoked by chloroquine or SLIGRL-NH2, and vice versa. Notably, blocking

itch-generating fibers did not reduce pain-associated behavior. However, silencing TRPV1+ or TRPA1+ neurons allowed AITC or capsaicin respectively to evoke itch, implying that certain peripheral afferents may normally indirectly inhibit algogens from eliciting itch. These findings support the presence of functionally distinct sets of itch- and pain-generating neurons and suggest that targeted silencing of activated sensory fibers may represent a clinically useful anti-pruritic and analgesic therapeutic approach.

RECEPTORS, CHANNELS AND NEURAL PATHWAYS OF ITCH

IL10

A NEW SIGNALING PATHWAY BETWEEN EPITHELIAL CELLS AND NEURONS TRIGGERS ITCH VIA THE ATOPIC DERMATITIS CYTOKINE TSLP

Lydia The, Sarah Wilson, Katherine Beattie, [4]Maurizio Pellegrino, Lyn Batia, George Katibah, Daniel Estandian, Diana Bautista

UC Berkeley, Berkeley, CA, USA

Atopic dermatitis (AD) is a chronic itch disorder of the skin that affects one in ten people. Patients suffering from severe AD eventually progress to develop asthma and allergic rhinitis, in a process known as the "atopic march." Signaling between epithelial cells and innate immune cells via the cytokine Thymic Stromal Lymphopoietin (TSLP) is thought to drive AD and the atopic march. Here we report that epithelial cells directly communicate to sensory neurons via TSLP to promote itch. We identify the ORAI1/NFAT calcium signaling pathway as an essential regulator of TSLP release from keratinocytes, the primary epithelial cells of the skin. TSLP then acts directly on a novel subset of sensory neurons to trigger robust itch behaviors. These data support a new model whereby calcium-dependent TSLP release by keratinocytes activates both primary afferent neurons and immune cells to promote inflammatory responses in the skin and airways.

IL11

THE ROLE OF MRGPRS IN ITCH

Xinzhong Dong

Johns Hopkins University School of Medicine

We identified a large family of G protein-coupled receptors in mice called Mrgprs. Many of these receptors are exclusively expressed in distinct subsets of small-diameter dorsal root ganglion (DRG) neurons. We found that MrgprA3 functions as a receptor for chloroquine (an anti-malaria drug) and is required for chloroquine-induced itch. Besides chloroquine, Mrgprs also respond to several itch-inducing compounds such as BAM8-22, SLIGRL, and beta-alanine suggesting that Mrgprs are novel itch receptors by directly sensing these compounds. Our preliminary data have shown the involvement of Mrgprs in mouse chronic itch models such as dry skin, contact dermatitis, and allergic itch. Importantly, some of the results have been confirmed in human psychophysical studies. In addition, we have genetically labeled and manipulated Mrgpr-expressing neurons in DRG and showed these neurons defined itch-mediating primary sensory neurons with specific projection pattern in the skin and electrophysiological properties. Therefore, we believe that targeting Mrgprs may lead to novel treatment of chronic itch in the future.

IL12

NPPB IS CRITICAL FOR ITCH

Mark Hoon

National Institute of Dental and Craniofacial Research, NIH, Bethesda, MD, USA

The mechanisms by itch sensation is transmitted is still poorly understood, although recently it was shown that the neuropeptide GRP is required for these responses. We determined that another peptide Nppb is expressed in a subset of TRPV1-peripheral sensory neurons which contain the itch receptor MrgprA3. In order to examine its role *in vivo* we generated knockout animals and found that while Nppb null mice exhibit normal behavior to thermal and painful stimuli, they displayed profoundly reduced scratch-reaction to all pruritic agents tested. Intrathecal administration of Nppb was sufficient for itch-behavior and suggests that Nppb is a primary transmitter of pruritic signals. Ablation of Nppb-receptor interneurons causes specific itch deficits but does not alter those elicited by intrathecal administration of GRP, indicating that Nppb is a transmitter (or neuromodulator) upstream of GRP. Additional studies established that GRP is expressed in Nppb-receptor dorsal horn neurons. Thus we demonstrate that Nppb is an essential primary transmitter of a dedicated itch pathway.

IL13

SPECIFIC ITCH PATHWAYS: HOLY GRAIL FOR CLINICAL PRURITUS?

Martin Schmelz

Department of Anesthesiology Mannheim, Heidelberg University, Heidelberg, Germany

We have seen tremendous progress in the characterization of specific neuronal pathways for itch in rodents and humans over the last years. While it might appear that following this direction of research directly leads to the identification of the clinically relevant pathways in chronic itch patient we also have to take into consideration the alternative hypothesis, i.e. itch generation by activation of itch-specific patterns of nociceptors. The itch-specific patterns in nociceptors are defined by network activity of neurons rather than on defined signalling pathways and therefore their analysis cannot be directly addressed by standard genetic approaches. We therefore crucially need mechanistic information from chronic itch patients that guide our therapeutic research towards identification of specific signalling cascades in pruriceptors and towards identification of mechanism that drive itch-specific network activity in nociceptors. Ultimately, both approaches are equally promising to generate successful anti-pruritic therapy, but translational studies in patients based on our mechanistic knowledge are required to provide the pivotal information validating targets directly in chronic itch patients.

BASIC RESEARCH TRACK: INHIBITORY PATHWAYS

IL14

SPINAL DYNORPHIN MODULATES ITCH

[1]Sarah Ross, [2]Adam Kardon, [2]Erika Polgar, [2]Lindsey McClement, [2]Junichi Hachisuka, [2]Erica Schwarz, [2]Christopher Fan, [2]Gregory Hemenway, [2]Nagase Sergei Karnup, [2]Andrew Todd

[1]Department of Neurobiology, Pittsburgh Center for Pain Research, University of Pittsburgh, Pittsburgh, PA, [2]University of Pittsburgh, USA

Scratching and other counter-stimuli provide relief from itch that persists for minutes. However, the neural basis for the inhibition of itch by counter-stimuli is unclear and the neuromodulatory mechanisms underlying the anti-pruritic state are completely unknown. We now identify spinal B5-I interneurons as key neurons that function to inhibit itch. Acute inhibition of B5-I neurons results in spontaneous scratching. Moreover, B5-I neurons release dynorphin, an endogenous kappa opioid receptor agonist. Our data indicate that kappa agonists are selective for itch and bidirectionally modulate itch at the level of the spinal cord. Finally, through whole-cell patch clamp recording we show that B5-I inhibitory neurons receive direct inputs from menthol-, capsaicin- and AITC-responsive sensory neurons (those that express TRPM8-, TRPV1- and TRPA1-expressing primary afferents, respectively). These findings are consistent with the idea that B5-I neurons mediate the inhibition of itch by counter-stimuli and do so in part through the release of dynorphin. Thus, kappa agonists may inhibit itch just as mu agonists inhibit pain.

IL15

VGLUT2-REGULATED ITCH – PRIMARY AFFERENTS AND BEYOND

Malin Lagerström

Department of Neuroscience, Uppsala University, Uppsala, Sweden

The neurobiology of itch is under intense investigation. We have previously identified VGLUT2-mediated glutamatergic transmission as a crucial regulator of itch signaling from primary afferent neurons. Our studies have identified a prominent role for TRPV1 primary afferent neurons in itch regulation as deletion of Vglut2 from TRPV1 neurons resulted in profound itch leading to the development of wounds on the neck and face. Deletion of Vglut2 from primary afferent neurons, using the Ht-Pa Cre line, resulted in similar itch behavior leading us to conclude that the itch phenotype originates from peripherally located TRPV1 neurons. Moreover, the glutamate deficient phenotype could be attenuated by anti-histamines but not Substance P antagonist treatment, showing that glutamate-deficient itch has a histaminergic origin and does not depend on SP-mediated transmission. We now show that deficiency of VGLUT2-mediated regulation of itch through TRPV1 neurons is reversed by genetic deletion of the gastrin releasing peptide receptor (GRPR) or GRPR antagonist treatment, corroborating the role of GRPR expressing neurons in the spinal cord in itch transmission. We are using mouse genetics, electrophysiology, *in vivo* 2-photon microscopy and optogenetics to understand how glutamate is regulating itch and which neurotransmitters and neuronal populations in the spinal cord regulate and transmit this sensation.

IL16

A SEMAPHORIN STORY IN ATOPIC DERMATITIS

Kenji Takamori

Institute for Environmental and Gender Specific Medicine, Juntendo University Graduate School of Medicine Department of Dermatology, Juntendo University Urayasu Hospital, Japan

Nerve density in the epidermis may be involved in itch sensitization in pruritic skin diseases such as atopic dermatitis. Epidermal innervation is thought to be regulated by a fine balance between nerve elongation factors and nerve repulsion factors. Class 3 semaphorins, a family of secreted proteins, have been implicated in a variety of biological functions, and were originally identified as axonal guidance cues during neural development. Sema3A is the first member of this family shown to cause growth cone collapse in neurons, i.e., to function as a nerve repulsion factor. Interestingly, Sema3A has been found to inhibit NGF-induced sprouting of sensory nerves, whereas elevated levels of NGF reduced the Sema3A-induced collapse of sensory growth cones. We previously found that epidermal Sema3A levels were lower in patients with atopic dermatitis than in healthy controls, concomitant with an increase in epidermal nerve density. Althoug the mechanism regulating the Sema3A gene has not yet been determined, these indicate good correlations between epidermal innervation and Sema3A levels. In addition, treatment with Sema3A replacement and other treatments such as UV-based therapies normalized the hyperinnervation. These findings may expand the knowledge of potential therapeutic strategies for ameliorating pruritus in patients with atopic dermatitis.

CLINICAL RESEARCH TRACK: BURDEN OF ITCH

IL17

THE BURDEN OF ITCH

Suephy Chen, Brittany Leader, Chris Carr, Emir Veledar

Department of Dermatology, Emory University, Atlanta, USA

The burden of pruritus can be understood by the magnitude of the problem as well as the impact of the symptom on those who suffer with it. In this talk, we will review the known prevalence of pruritus as well as understand the quality of life impact of pruritus. We will also discuss best ways to measure the economic impact of pruritus. This talk will focus not only on the data published in the literature, but also key concepts in methodology to measure burden.

IL18

THE BURDEN OF ITCH AMONG DERMATOLOGICAL PATIENTS IN EUROPE

[1]Florence Dalgard, [2]Joerg Kupfer, [1]Jon Anders Halvorsen

[1]University of Oslo, Oslo, Norway, [2]University of Justus-Liebig, Giessen, Germany

Introduction: Itch is a major symptom among dermatological patients and yet the impact on patients' lives has been difficult to assess. *Objectives:* To assess the burden of itch among dermatological patients in Europe by estimating the quality of life

and depression among patients reporting itch. *Material and Methods*: The design is cross-sectional. In dermatological clinics in 13 countries in Europe, a questionnaire was filled in by 250 consecutive patients and 125 healthy controls. The questionnaire included sociodemographic background information, an item on the presence of itch or not, and if yes the duration and intensity of itch assessed with a visual analogue scale. Additionally the following questionnaires were filled in: Eq5D, DLQI and the Hospital Anxiety and Depression Scale. A clinical examination was performed. *Results*: The total number of responders was 4994. The patients reporting itch were more depressed than those without itch (13% vs 5%), had more anxiety (21% vs 12%), had more limitation on all items of the EQ5D, and had more large impact on DLQI (60% vs 25%) *Conclusions*: This study demonstrates the burden of itch on patients reporting this symptom by showing the association with depression, anxiety and quality of life.

BASIC RESEARCH TRACK: SKIN AND SPINAL CORD MECHANISMS OF ITCH

IL19

GASTRIN-RELEASING PEPTIDE (GRP) IS CRITICAL FOR MEDIATING LONG-LASTING ITCH IN SENSORY NEURONS

Zhou-Feng Chen

Center for the Study of Itch, Department of Anesthesiology, Washington University School of Medicine Pain Center, St. Louis, MO, USA

In this talk, I will report that constitutive activation of the BRAF pathway in Nav1.8+ neurons of mice (BRAFNav1.8 mice) results in spontaneous scratching behavior. By contrast, these mice maintain normal responses to a wide range of noxious stimuli. Remarkably, BRAFNav1.8 mice show dramatic ectopic expression of gastrin-releasing peptide (GRP) in DRG neurons and GRPR, along with pERK, in the spinal cord, the latter of which probably reflects a central sensitization of itch signaling consequent to persistent amplified pruriceptive inputs. These molecular changes are recapitulated in mice with allergic contact dermatiti – or dry skin-elicited itch. Importantly, chronic itch of these mice is markedly attenuated by a GRP blocker (77427) or by genetic ablation of GRP or GRPR in mice. These data underscore the importance of GRP as an itch-specific peptide in the development of chronic itch and identify the RAF-MEK-ERK pathway as an upstream regulator that confers a subset of nociceptors with novel pruriceptive properties to initiate and maintain long-lasting itch sensation.

IL20

STUDIES OF PRURICEPTIVE RESPONSES OF TRIGEMINOTHALAMIC TRACT NEURONS IN RATS

Hannah Moser, Glenn Giesler

Department of Neuroscience, University of Minnesota, USA

Chronic itch syndromes are common and often affect the face. We wished to examine the mechanisms underlying itch in this region. We found that about half of the 103 examined rat trigeminothalamic tract (VTT) neurons were activated by intradermal facial injections of one or more pruritogens. The response durations matched those of scratching produced by the same pruritogens in awake rats, suggesting that VTT neurons contribute to sensation of itch. Each pruriceptive neuron (P-N) also responded to noxious mechanical. Intrathecal application of morphine is a powerful method used to treat severe pain. However, opiates commonly produce severe itch, limiting treatment. The neurons responsible for opiate-induced itch have not been identified. We observed that intrathecal morphine increased ongoing firing of P-N VTT neurons, increased their responses to itch-producing stimuli (hyperknesis), and increased responses to innocuous mechanical stimuli (alloknesis). These effects were not observed for non-pruriceptive VTT neurons. In neurons that responded only to noxious stimuli, the same dose of morphine reduced responses to noxious pinch but did not affect responses to innocuous stimuli. Our results identify two populations of VTT neurons which are differentially affected by morphine, and help explain several aspects of analgesia and opiate-induced itch.

BASIC RESEARCH TRACK: ANIMAL MODELS: RODENTS, CANINES AND PRIMATES

IL21

MURINE MODELS OF ITCH AND PAIN IN HUMANS

[1]Robert LaMotte, [1]Lintao Qu, [1]Parul Sikand, [1]Ni Fan, [1,2]Chao Ma, [3]Steven Shimada, [4]Liang Han, [4]Xinzhong Dong, [1,2]Tao Wang, [1,5]Kai Fu, [1,5]Hong Nie, [1]Brett King

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The mouse is commonly used for molecular-genetic and cellular studies of chemically evoked itch and pain. How do we know whether the chemically elicited biological measurements in mice relate to itch or other sensory qualities such as pain? One approach is to measure chemically evoked itch and nociceptive sensory qualities in humans and then determine how the same stimuli are behaviorally differentiated when applied to the mouse. For example, injected into normal skin of humans, histamine elicits more itch than pain, and capsaicin has the opposite effect. In the mouse, histamine vs. capsaicin evoked different types of site-directed behaviors when applied to either the cheek (scratching vs. wiping) or to the calf of the hind limb (biting vs. licking). Interestingly, in allergic contact dermatitis (ACD), challenge with a contact sensitizer leads to increased stimulus-evoked itch and pain in humans and analogous behaviors in mouse. In mice, electrophysiological recordings from pruriceptive, transgenically-labeled, sensory neurons, visualized both *in vitro* and, in the intact ganglion *in vivo*, revealed signs of hyperexcitability that might contribute to the enhanced itch and pain of ACD.

IL22

INHIBITORY EFFECTS OF DYNORPHIN-A ON SPINALLY ADMINISTERED BETA-ENDORPHIN- AND GRP-INDUCED SCRATCHING IN NONHUMAN PRIMATES

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[1]Department of Anesthesiology and Pain Medicine School of Medicine, Ewha Womans University, Seoul, South Korea, [2]Department of Physiology & Pharmacology, Wake Forest University School of Medicine, Winston-Salem, USA

Endogenous opioid peptides have been implicated in itch (pruritus) in patients with diverse systemic diseases. In addition, recent studies suggest that gastrin-releasing peptide (GRP) and its receptor (GRPR) are involved in the neurotransmission of itch and they are up-regulated in patients with chronic skin disease. The aim of the study was to characterize the magnitude and duration of scratching responses elicited by spinal beta-endorphin and GRP, and to investigate effects of antagonists and kappa opioid receptor-preferring peptide dynorphin-A on these endogenous ligand-induced scratching in monkeys. After intrathecal administration, both beta-endorphin (10–100 nmol) and GRP (1–10 nmol) dose-dependently elicited similar, profound scratching responses which last for 1–2 h. When a mu opioid receptor antagonist naltrexone (30–100 nmol) was administered intrathecally, naltrexone attenuated beta-endorphin- but not GRP-induced scratching. In contrast, when a GRPR antagonist RC-3095 (30–100 nmol) was administered intrathecally, RC-3095 was effective in blocking GRP-, but not beta-endorphin-induced scratching. Furthermore, intrathecal dynorphin-A significantly attenuated both beta-endorphin- and GRP-induced scratching. These findings indicate that spinal mu opioid receptor and GRPR are two independent receptor mechanisms mediating itch and that dynorphin-A, like most kappa opioids, is able to attenuate scratching elicited by different pruritogens in primates.

IL23

MODELING ATOPIC ITCH AND SKIN LESIONS IN DOGS: ALLERGEN CHALLENGES IN HYPERSENSITIVE DOGS OFFER OPTIMAL TRANSLATION POTENTIAL

Thierry Olivry

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In spite of itch being the most common dermatological problem seen in dogs, its experimental induction has proven to be difficult in this species. While the intradermal injections of histamine, serotonin, tryptase, substance P, IL-2, or mast cell-degranulating anti-IgE antibodies all initially failed to induce itch in dogs, recent studies have shown that recombinant canine IL-31 and proteolytically active cowhage can induce pruritic manifestations in dogs. However, modeling itch with the activation of single pathways is fraught with the risk that interventions tested using these activators might not necessarily correlate with clinical efficacy in itchy dogs because of pruritogenic pathway redundancy. To alleviate this possible lack of reliable translation of experimental findings to allergic patients, more complex models have been developed, which involve dogs sensitized to clinically relevant food, fleas or house dust mite allergens; these models have the advantage of closely reproducing both clinical and immunological characteristics of spontaneously-arising canine atopic dermatitis. As a result, experimental models involving allergen challenges in hypersensitive dogs, which reproduce both itch and skin lesions, appear to offer the optimal translatable potential not only for canine, but also for human atopic pruritus and skin lesions.

PARANEOPLASTIC ITCH

IL24

PARANEOPLASTIC ITCH

[1]Ben Zylicz, [2]Melanie Weiss, [3]Thomas Mettang, [2]Elke Weisshaar

[1]Hidegard Hospice Basel, Switzerland, [2]Department of Clinical Social Medicine, Occupational and Environmental Dermatology, University of Heidelberg, [3]German Hospital for Diagnostics, Nephrology, Wiesbaden, Germany

Paraneoplastic itch is a rare symptom that sometimes complicates malignant diseases. The frequency of this symptom is unclear, epidemiological data in this field are missing. The symptom seems to appear rather rarely, which may be explained by its heterogeneous and often unclear pathophysiology. Patients with both, haematological and solid tumour malignancies can be affected. So far, there is no clear definition of paraneoplastic itch. One must assume that paraneoplastic itch, due to the insufficient data and knowledge situation, does not receive the required attention among physicians. Adding to this is the fact that it usually appears with normal skin but itch in these patients can also occur with skin lesions due to the increased frequency of e. g. adverse drug reactions in this group of patients. All this explains why treatment of paraneoplastic itch still forms a challenge. In 2012, an interdisciplinary study group of dermatologists, internal specialists and social scientists was founded, striving to elaborate a clear definition of paraneoplastic itch and to comprise updated diagnostics and treatment. A clear definition of paraneoplastic itch is supposed to offer better and more focused diagnostics, to inspire clinical studies and to optimize possibilities of treatment.

SCORING IN CLINICAL TRIALS

IL25

UPDATE ON TOOLS FOR ITCH ASSESSMENT

Matthias Augustin

Hamburg, Germany

No abstract is provided.

IL26

DETERMINATION OF MINIMUM CLINICALLY IMPORTANT DIFFERENCE (MCID) OF VISUAL ANALOGUE SCALE (VAS): IN WHICH DIRECTION SHOULD WE PROCEED?

[1]Adam Reich, [1]Karolina Medrek, [2]Sonja Stander, [1]Jacek C. Szepietowski

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Pruritus measurement remains a challenge. Assessment of pruritus severity using VAS is frequently used in clinical trials. How-

ever, it is still unclear, to which extend pruritus must improve, to consider the change as clinically meaningful. To determine the MCID of VAS in pruritus evaluation we performed a study involving 161 patients (74 females and 87 males, mean age: 48.7±17.6 years) suffering from dermatological pruritus. Each patient received a standard dermatological care depending on the underlying skin disease. Pruritus was assessed at baseline, week 2 and week 6. Verbal Rating Scale (VRS) of pruritus severity and Dermatology Life Quality Index (DLQI) served as external measures. The absolute difference between two VAS measurements enabling a patient to change the severity category by one point in VRS or DLQI was 1.5 and 1.7 points, respectively, while the relative difference was 24% and 18%, respectively. Relative VAS change compared to absolute VAS difference better correlated with DLQI change (ρ=0.4 vs. ϱ=0.33), DLQI at week 2 (ρ=–0.31 vs. ϱ=–0.15) and DLQI at week 6 (ρ=–0.43 vs. ϱ=-0.41). Based on achieved results it seems that VAS scoring should change of at least 20% (VAS20) to consider the antipruritic therapy as, at least minimally, effective.

IL27

PRURIGO NODULARIS: INTRODUCTION OF A RE-DEFINED CLASSIFICATION AND PRURIGO ACTIVITY SCORE (PAS)

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Prurigo describes a scratch-related reaction pattern in chronic pruritus. Prurigo nodularis (PN) is used to designate a prurigo in which nodules are present. However, lesions in prurigo do not have a uniform appearance, but include a broad range of lesional types. Currently, no unifying terminology is available and no activity scores exist. The aim of our study was to develop a classification and a tool to monitor PN patients during therapy in clinical trials and daily routine. In an expert panel, we discussed and re-defined the clinical features of PN. Prurigo can be defined by (a) the clinical type of lesions (papules, nodules, plaques, ulcers), (b) activity (presence of excoriations or scars) and (c) number of lesions. In view of the very large number of lesions running into hundreds (mean, 180±146; median, 108.5) that might be present, in clinical trials, it would not be practicable to count the lesions for assessing disease severity and monitoring patients. Therefore, we defined a prurigo activity score (PAS), which includes besides other items a grading system (Grade I–IV: <25%, 25–49%, 50–75%, >75% active scratch lesions) and a method for measuring marker lesions. The new prurigo terminology is currently under evaluation and needs further validation.

NEUROPATHIC ITCH SYNDROMES

IL28

NEUROPATHIC ITCH SYNDROMES: OVERVIEW AND OPPORTUNITIES

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Dermatologists are increasingly aware that some unexplained chronic itch is caused by neurological disease, but few dermatologists or neurologists feel well-informed. Neuropathic itch (NI) can be divided into widespread and focal cases. Small-fiber polyneuropathy (SFPN) is the most common cause of widespread NI, with or without other symptoms. SFPN usually begins in the feet but can spread proximally, and sensation can be preserved. Patchy or total-body symptoms are associated with autoimmune sensory ganglionitis. SFPN is best managed by treating its causes, whether nutritional, malignant, autoimmune, neurotoxic or infectious, and diagnosis may require neurodiagnostic skin-biopsy. Central NI from brain or spinal-cord lesions usually presents with unilateral or dermatomal focal itch, but the spongiform encephalidites can cause widespread itch. Common causes of focal NI include shingles and compression of nerve roots or nerve branches (notalgia paresthetica and brachioradial pruritus). A rostrocaudal gradient leaves the head and neck particularly susceptible. Cases in which colocalizing NI and sensory loss produce facial self-mutilation from scratching are historically known as trigeminal trophic syndrome. NI does not respond to antihistamines or anti-inflammatories. Local anesthetics are a treatment mainstay, along with behavioral modification. Symptoms due to compression may be relieved by surgery. However new treatment options are needed.

ITCH CLINICS

IL29

UPDATE ON THE ANTIPRURITIC EFFECT OF APREPITANT

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Aprepitant is a neurokinin-1 receptor (NK1R) antagonist with antipruritic effect in acute and chronic pruritus as reported in many cases and two case series. We treated 62 patients (38 f, median age 68.5 years) with chronic pruritus of various origins by short- or long-term oral or single intravenous administration of aprepitant. A significant pruritus reduction was found in the whole study group. The best results were observed in prurigo nodularis (PN; VAS 7.0±2.1 to 4.5±2.8; p=0.000004) independent of the presence or absence of atopic predisposition. In order to investigate the underlying mechanisms of antipruritic effect in

PN, immunohistology, PCR and western blot were performed in skin biopsies before and after therapy. Aprepitant led to a reduction of CD5, CD25- and IL-17-positive T lymphocytes. The expression of the NK1R was found to be up-regulated in PN compared to healthy controls prior to therapy; western blot showed no significant change in the regulation of the receptor after therapy. However, immunohistological staining revealed epidermal up-regulation of NK1R in patients treated for 4 weeks with aprepitant. In sum, aprepitant therapy leads to a change in the inflammatory infiltrate and epidermal increase of the NK1R supporting the hypothesis of cutaneous effects of the substance.

IL30

ITCH AND SLEEP - USE OF A NONWEAR ACTIGRAPHY FOR THE DETECTION OF ITCH AND SLEEP IN PATIENTS WITH CHRONIC ITCH

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Severe itch frequently induces sleep disturbance. Scratching while asleep tends to be vigorous because of the lack in voluntary inhibition, leading to the exacerbation of skin lesions. Scratching also plays a major role in arousal from sleep. Since scratching occurs more frequently during the light stages of sleep, a vicious cycle between sleep disturbance and worsening of skin lesions is formed. Therefore, it is important to consider the condition of sleep in treating patients with chronic itch. Wrist actigraphy has been widely used for detecting sleep-wake states in clinical setting. However, the result of the measurement is influenced by scratching because the motions of the hands in scratching even while asleep are regarded as “awake” in this manner. We examined a nonwear actigraphy (NWA) device for the evaluation of sleep in patients with chronic itch. The NWA device has a highly sensitive pressure sensor placed under a mattress and continuously records the activities of an individual lying on the mattress. The characteristics of NWA in comparison with wrist actigraphy will be presented. The results of sleep monitoring also revealed irregular sleep habits of some patients with chronic itch, suggesting the need for lifestyle intervention.

CLINICAL RESEARCH TRACK: METHODOLOGY FOR CLINICAL RESEARCH IN ITCH

IL31

USING PLACEBO EFFECTS FOT ITCH AND PAIN: PSYCHOPHYSIOLOGICAL MECHANISMS AND THERAPEUTIC STRATEGIES

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Itch shares common neurophysiological and psychophysiological processes with pain, when studying for example sensitization processes and related placebo effects in both symptoms. However, research in this area on itch has received far less attention than in pain. In this lecture, recent evidence on the psychophysiological similarities and differences between itch and pain will be presented, with a focus on both mechanisms and therapeutic strategies, particularly in the area of placebo effects. Specifically, an overview about our recent psychophysiological studies will be given, focusing particularly on cognitive expectancy mechanisms (e.g. conditioning) and demonstrating both common and distinctive psychophysiological mechanisms and therapeutic strategies for chronic itch and pain. Implications for possible common therapeutic strategies using placebo mechanisms, e.g. for increasing adherence strategies, will be discussed.

IL32

SKIN BIOPSIES FOR EVALUATING THE NEURAL COMPONENT OF ITCH

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The neural component of inflammatory dermatoses is receiving increased attention. The importance of thick versus thin sections and choice of antibodies to visualize cutaneous sensory nerve fibers by immunohistochemistry will be discussed.

ABSTRACTS: Free Communications (FC01–FC42)

BASIC RESEARCH TRACK: INHIBITORY PATHWAYS

FC01

SPINAL INTERNEURONS MEDIATE THE INHIBITION OF ITCH BY COUNTER-STIMULI

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There is empirical evidence that noxious and/or cooling stimulation of the skin can attenuate itching. However, the neural basis for the inhibition of itch by counter-stimuli is unknown. We previously discovered that the developmental expression of the transcription factor Bhlhb5 marks a population of spinal interneurons that may function to inhibit itch. Here we tested the hypothesis that these spinal interneurons mediate the inhibition of itch by counter-stimuli. To test this idea, we made whole-cell patch clamp recording from Bhlhb5 positive neurons in the superficial dorsal horn. The inhibitory subset of these neurons (B5-I neurons) was identified based on its response to somatostatin. Since menthol and noxious irritants such as capsaicin and AITC inhibit itch, we next investigated whether B5-I neurons receive inputs from menthol-, capsaicin- and AITC-responsive sensory neurons. Approximately 80 % of B5-I neurons showed a significant increase the frequency of excitatory post-synaptic currents (EPSCs) upon application of capsaicin, AITC or menthol. Moreover, this increase in EPSC frequency was not blocked by tetrodotoxin, indicating that B5-I neurons receive monosynaptic input from primary afferents that respond to cool or noxious chemicals. These findings are consistent with the idea that B5-I neurons mediate the inhibition of itch by counter-stimuli.

FC02

CIGUATOXIN-INDUCED RELEASE OF NEUROPEPTIDES IN A SENSORY NEURON-KERATINOCYTE COCULTURE MODEL

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Ciguatera fish poisoning (CFP) is caused by eating tropical and subtropical fishes contaminated by ciguatoxins (CTXs). The most characteristic manifestations are cutaneous sensory signs, including paresthesia, cold-induced dysesthesia and pruritus, which can persist for several months. CFP-associated itch is poorly understood and typically not relieved by antihistamine drugs. CTXS are known to bind to voltage-gated sodium channels (Nav) leading to Na+ entry and increased excitability in various cell types including secretory neurons. Recently, CTX-induced cold allodynia in mice has been shown to involve the TRPA1 channel in CGRP-positive sensory neurons. CGRP-positive unmyelinated sensory neurons have been involved in both histamine-dependent and histamine-independent itch pathways, with TRPA1 associated with the latter. The aim of this study was to measure the release of the neuropeptides substance P (SP) and CGRP in a coculture of human keratinocytes and rat DRG neurons exposed to Pacific-CTX-2. We showed that low nanomolar concentrations of P-CTX-2 cause a large release of SP and CGRP in this model. Using pharmacological tools, we studied the involvement of a number of targets, including Nav, selected TRP channels and the PAR-2 receptor, in this CTX-induced release. The results of this work provide some molecular basis to elucidate mechanisms underlying CTX-induced itch.

FC03

ENIGMATIC ASPECTS OF 5'-GNTI-INDUCED COMPULSIVE SCRATCHING IN MICE

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5'-Guanidinonaltrindole (5'-GNTI), the kappa opioid receptor antagonist, precipitates repetitive neck scratching after s.c. injection into the neck of S.W. mice. In terms of potency and efficacy: 5'-GNTI>6'-GNTI (regioisomer)>/=norbinaltorphimine (norBNI)>natriuretic polypeptide b (0.3-5 mg/kg). 5'-GNTI is not active by i.th. (lumbar) or icv routes. Tolerance did not develop to the scratching when 5'-GNTI (0.3 mg/kg) was given to mice once daily for 8 consecutive days. 5'-GNTI (0.3 mg/kg) still elicited excessive scratching in mice lacking mu, delta or kappa opioid receptors, respectively, as well as in mice pretreated with either norBNI (20 mg/kg, i.p. at –18 hr) or naloxone (10 mg/kg, i.p.). Neither the histamine-1 receptor antagonist, fexofenadine (20–60 mg/kg, p.o.) nor the histamine-4 antagonist, JNJ 10191584 (10–60 mg/kg, p.o.) attenuated 5'-GNTI-induced scratching. Thus, the pharmacological basis of GNTI-evoked scratching is unknown. Nonetheless, the robust syndrome is of interest to basic scientists as a compelling behavior in its own right, as well as providing an experimental model for potential drug discovery in psycho- and dermatopharmacology. (Supported by NIDA #DA13429). patients reporting this symptom by showing the association with depression, anxiety and quality of life.

CLINICAL RESEARCH TRACK: BURDEN OF ITCH

FC04

PRIMARY LOCALIZED CUTANEOUS AMYLOIDOSIS - ASSOCIATION WITH ATOPIC DERMATITIS

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Objectives: To assess if atopic dermatitis (AD) is more prevalent in patients with primary localized cutaneous amyloidosis (PLCA) compared to patients with other conditions. Secondarily, to investigate if the prevalence of AD, severity of itch, morphology and locations of PLCA differ between familial and sporadic forms. *Methods:* Consecutive patients with the clinical diagnosis of PLCA visiting a dermatology clinic were evaluated by a single investigator. Data on demographics, family history, morphological types and locations of PLCA, and itch score were collected and

they were screened for concomitant AD based on history and physical examination. The control population consisted of consecutive patients with diagnoses other than PLCA who attended the same clinic. *Results:* Forty-four patients with PLCA and 97 controls were evaluated. The prevalence of AD in patients with PLCA was significantly higher than in controls, at 75% and 39.2%, respectively (OR=4.66, 95% CI=2.10–10.3, $p<0.0005$). The prevalence of AD in sporadic cases was significantly higher than familial cases, at 84.4% and 50% respectively (OR=5.4, 95% CI=1.23–23.7). Mean itch levels, morphological types and locations of PLCA did not differ between familial and sporadic cases. *Conclusions:* AD was associated with PLCA and the association was stronger with the sporadic compared to the familial cases.

FC05

INFLUENCE OF SCRATCH LESIONS AND PRURITUS LOCALIZATION ON PSYCHIC SYMPTOMS

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Introduction: Chronic Pruritus (CP) is often associated with psychic symptoms like anxiety or depression or influenced by psychic co-factors. Until now, there is only little knowledge about how the presence of scratch lesions and CP localization (localized, generalized) correlate to these symptoms. *Methods:* We examined 619 patients with CP. The itch intensity was detected via visual analogue scale (VAS, 0 to 10). Besides a dermatological examination patients filled in the Hospitality Anxiety and Depression Scale (HADS). Statistics were performed by t-test for independent variables and one-way ANOVA. *Results:* Patients with scratch lesions had significantly higher scores in both HADS subscales (depression (p=0.02), anxiety (p=0.05)) than patients with no visible lesions. VAS or HADS scores were not different between patients with initially localized and initially generalized pruritus. Patients who reported that their CP became generalized from initially localized pruritus or with primarily generalized CP reported significantly higher scores of anxiety (p=0.028), depression (p=0.002) and pruritus intensity (p=<0.0001) in contrast to patients with remained localized pruritus. *Conclusion:* The presence of scratch lesions and CP course concerning the localization are important factors for the development of psychic symptoms. Whether psychic symptoms are reversible when the CP and scratch lesions improve, needs further exploration.

FC06

NEEDS OF HEMODIALYSIS PATIENTS SUFFERING FROM CHRONIC ITCH: RESULTS FROM PATIENT INTERVIEWS

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Itch is a symptom with substantial impact on Quality of Life (QoL) that is frequent in patients relying on hemodialysis. These patients already suffer from strong limitations in everday life, but yet it is not much known about additional impairment through itch in these patients. Semi-structured interviews were conducted in 10 affected patients to assess their feelings and conditions concerning subjective perception of chronic itch, characteristics of the symptom as well as itch-treatment, coping and health care. We also asked them to complete existing standardized questionnaires addressing QoL in patients with kidney disease as KDQOL to gather their opinion concerning these questionnaires. Here we present data on analyzed qualitative patient-interviews conducted with hemodialysis-patients with and without chronic itch as well as chronic itch patients without present kidney disease. All patients stated to suffer from underestimation of the symptom through physicians and reported problems such as side-effects with prescribed treatment. Also dissatisfaction with a questionnaire frequently used in kidney diseases could be shown. These results demonstrate impairment in QoL and help to better identify needs of hemodialysis-patients suffering from chronic itch. They may improve research in this difficult group of patients as they for example provide indications to develop patient-oriented questionnaires.

FC07

NEUROTICISM ASSOCIATED WITH GREATER QUALITY OF LIFE IMPACT OF CHRONIC ITCH

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Of the 5 main personality factors – neuroticism, agreeableness, conscientiousness, openness, extraversion – neuroticism has been implicated in the reporting of high levels of chronic itch. 10 personality 'styles' can be conceptualized by the intersection of each personality factor (e.g. neuroticism vs. conscientiousness yields style of impulse control.) A convenience sample of 110 adult (≥18 years) subjects with chronic pruritus >6 weeks affiliated with the National Eczema Association completed validated questionnaires to assess characteristics of their pruritus (ItchyQoL) and personality traits (NEO-Five Factor Inventory). The 110 subjects in the final dataset were mostly (82%) female, 72% endured symptoms >10 years and 40% reported their pruritus to be 'severe'. Fisher's LSD t-test was used to perform multiple pairwise comparisons of mean ItchyQoL score between each of the four subgroups of the 10 personality styles. Among all four personality styles where neuroticism contributes – impulse control (neuroticism vs. conscientiousness), anger control (neuroticism vs. agreeableness), defense (neuroticism vs. openness), (well-being neuroticism vs. extraversion) – a significantly greater ItchyQoL score was determined by degree of neuroticism, irrespective of the other personality factor. Whether the degree of neuroticism drives perception of QoL impact of pruritus or is a consequence of chronic itch remains to be elaborated.

BASIC RESEARCH TRACK: SKIN AND SPINAL CORD MECHANISMS OF ITCH

FC08

A SUBPOPULATION OF NOCICEPTORS SPECIFICALLY LINKED TO ITCH

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Itch-specific neurons have been sought for decades. The existence of such neurons has been doubted recently as a result of the observation that itch-mediating neurons also respond to painful stimuli. We genetically labeled and manipulated MrgprA3+ neurons in the dorsal root ganglion (DRG) and found that they exclusively innervated the epidermis of the skin and responded to multiple pruritogens. Ablation of MrgprA3+ neurons led to substantial reductions in scratching evoked by multiple pruritogens and occurring spontaneously under chronic itch conditions, whereas pain sensitivity remained intact. Notably, mice in which TRPV1 was exclusively expressed in MrgprA3+ neurons exhibited itch, but not pain, behavior in response to capsaicin. Although MrgprA3+ neurons were sensitive to noxious heat, activation of TRPV1 in these neurons by noxious heat did not alter pain behavior. These data suggest that MrgprA3 defines a specific subpopulation of DRG neurons mediating itch. Our study opens new avenues for studying itch and developing anti-pruritic therapies.

FC09

TOLL-LIKE RECEPTOR 4 CONTRIBUTES TO DRY SKIN-INDUCED CHRONIC ITCH BUT NOT ACUTE ITCH IN MICE

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Itch (pruritus) is a common intractable symptom of several skin diseases, such as atopic dermatitis and xerosis. Toll-like receptors (TLRs) are well-known for mediating innate immunity by recognition of exogenous pathogen-associated molecular patterns (PAMPs) and endogenous danger-associated molecular patterns (DAMP). Recently, we have demonstrated the involvement of TLR3 and TLR7 in itch sensation in mice. In this study, we further examined the role of TLR4 in acute and chronic itch. We found that spontaneous scratching behavior in an experimental dry skin model was substantially decreased in male Tlr4−/− mice. In contract, acute scratching behavior induced by histamine and chloroquine was not affected in Tlr4−/− mice. Consistently, intrathecal injection of TLR4 antagonist lipopolysaccharide, derived from Rhodobacter sphaeroides (LPS-RS), had no effects on acute itch, but significantly reduced dry skin-induced chronic itch in mice. Furthermore, acute nociceptive pain, including mechanical and thermal pain was not affected in Tlr4−/− mice, whereas formalin-induced second-phase spontaneous pain was reduced in male Tlr4−/− mice. Our findings demonstrate distinct role of TLR4 in regulating acute itch and chronic itch in mice.

FC10

INTRADERMAL ENDOTHELIN-1 EXCITES BOMBESIN-RESPONSIVE SUPERFICIAL DORSAL HORN NEURONS IN THE MOUSE

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Electrophysiological methods were used to identify mouse superficial dorsal horn neurons responsive to intradermal (id) endothelin-1 (ET-1), and to test if they are excited by spinal superfusion of bombesin, a homolog of gastrin releasing peptide (GRP) that excites itch-signaling spinal neurons expressing the GRP receptor. In anesthetized mice a chemical search strategy identified ET-1-sensitive superficial dorsal horn neurons. They were then tested for mechanosensitivity, followed by bombesin (spinal superfusion; 200 μg/ml for 1 min), thermal and additional chemical stimuli (histamine, chloroquine, AITC, capsaicin). Of 46 ET-1-responsive units, 60% responded incrementally to brush and pinch (wide dynamic range), and 40% to pinch only (nociceptive specific). Most ET-1 responsive units also responded to noxious skin heating (94%), cooling (50%), id histamine (77%), id chloroquine (73%), AITC (86%) and id capsaicin (74%), and spinal superfusion of bombesin (57%). That the majority of ET-1-responsive neurons also responded to spinal bombesin suggests a role in the spinal transmission of itch. The majority of ET-1-sensitive spinal neurons also responded to additional pruritic and algesic stimuli, similar to histamine- and chloroquine-responsive neurons. Even though pruritogen-sensitive neurons also respond to noxious stimuli, we hypothesize that this neuronal subpopulation selectively encodes itch sensation.

CLINICAL RESEARCH TRACK: SYSTEMIC ITCH

FC11

AUTOTAXIN IN CHOLESTATIC ITCH; COMPARING MICE AND MEN

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Introduction: In patients with cholestasis, including intrahepatic cholestasis of pregnancy (ICP), serum autotaxin (ATX) activity correlates with itch intensity.1,2 We hypothesize that ATX causes itch by formation of lysophosphatidate, activating sensory nerve endings.1,3-5 AIM To establish a causal relationship between serum ATX and itch in mice. *Methods*: In mice we studied the effect of cholestasis by 1) bile duct ligation (BDL), 2) a 0.1% cholate diet in Atp8b1–/– mice and 3) during cholestatic pregnancy. We measured serum ATX activity and scratch activity during 12 hours. Immunohistochemistry for ATX and cell markers was performed on mouse and human tissues. *Results*: Serum ATX was very mildly induced by BDL (1.5-fold; p=0.003), cholate diet in Atp8b1–/– mice (2-fold; p<0.000) and pregnancy (2.5-fold; p<0.000). Cholestasis during pregnancy did not further enhance serum ATX. Scratch activity remained unaffected in all groups. Immunohistochemical analysis revealed strong ATX expression in human small intestinal enteroendocrine cells (EECs), which was absent in mice. *Conclusion:* Cholestasis induces serum ATX much less in mice, than in humans. Interestingly, this correlated with the absence of scratch behaviour in cholestatic mice. ATX expression in EECs as observed humans seems to be absent in mice, addressing a possible explanation for the much lower plasma ATX.

FC12

CUTANEOUS T-CELL LYMPHOMA AND PRURITUS: THE ROLE OF IL-31 IN THE SKIN

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Approximately 88% of cutaneous T-cell lymphoma (CTCL) patients are affected by intractable pruritus. IL-31, a cytokine produced by CD4+ Th2 cells, is involved in other pruritic skin diseases including atopic dermatitis. IL-31 signals through a receptor complex composed of IL-31RA and oncostatin M receptor β (OSMRβ), which has been implicated in another chronic itch skin disease, primary localized cutaneous amyloidosis (PLCA). Recently, IL-31 was shown to be elevated in serum of patients with CTCL and significantly higher in patients with marked pruritus. The aim of our study was to investigate the peripheral role of IL-31, IL-31RA, and OSMRβ in the skin of CTCL subjects with chronic itch. Cutaneous innervation and the expression pattern of these potential pruritic-mediators in the skin was correlated with the stage and type of CTCL and itch severity. IL-31 was found to be elevated ($p<0.05$) in nerve fibers in the epidermis and epidermal junction of patients with pruritic late stage Mycosis Fungoides and Sezary Syndrome CTCL when compaired to healthy controls. Furthermore, levels of IL-31 in the epidermis were found to significantly correlate with itch severity ($p<0.01$). These results may lead to the development of therapeutics to target CTCL-induced pruritus.

FC13

WHAT MAKES PEOPLE ITCH? A CROSS-SECTIONAL POPULATION BASED STUDY.

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Many people suffer from chronic pruritus (CP), but the evidence supporting published risk factors for CP is limited. To fill this void, we conducted a national survey of patients sampled from the U.S. Veterans Hospital Patient Database. In this sample, 403 patients suffered from CP; 670 patients did not. The patients with CP reported their itch severity of the past 7 days on a scale of one to ten, and completed a questionnaire assessing for diseases known to be pruritus risk factors. Two ordinal logistic regressions were performed: (1) with and without CP and (2) only those with CP. Itch severity, grouped into categories (none/low, medium, and high) was the outcome variable while demographic and disease categories (infectious, allergic, inflammatory, hepatic, endocrine, psych/neuro) were potential predictor variables. The presence of an allergic (parameter estimate: 1.3), inflammatory/autoimmune (1.2), or neurological/psychiatric (0.5) disease significantly ($p<0.001$) predicted pruritus severity when analyzing all patients. Among only CP patients, no disease category was a significant predictor of pruritus severity; only race was a significant predictor ($p<0.001$). These results suggest that while affliction with the above diseases increases the likelihood of having CP, the presence of such conditions is not a significant predictor of pruritus severity.

FC14

MESENTERIC MAST CELL DEGRANULATION AND OVEREXPRESSION OF TRPV1 AND PAR2 CONTRIBUTE TO PRURITUS IN BILE DUCT LIGATION RAT MODEL OF LIVER DISEASE

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Backgrounds and aims: Persistent pruritus is a recognized complication of cholestatic liver disease. The pathogenesis, including mediators and the underlying neuronal mechanism is poorly understood. In this study we examined a role of mesenteric mast cell degranulation and overexpression of TRPV1 and PAR2 in Bile Duct Ligation rat model of liver disease. *Methods:* After the mesentery fixation with Carnoy's solution, degranulated mesenteric mast cells were counted in sham and BDL rats. Scratching behavior was assessed in BDL and sham operated rats and we evaluated the effect of the compound such as gabexate mesilate, tryptase inhibitor, and TRPV1 and PAR2 antagonist on itch behavior. Western blot and immunohistochemistry were also performed. *Results:* BDL rats show degranulation of mesenteric mast cell, display enhanced scratching and over expression of TRPV1 and PAR2 in DRG neurons, concomitant with an increased proportion of small-diameter peptidergic neurons in comparison with sham operated rats. *Conclusion:* Chronic pruritus in liver disease is mediated by TRPV1 sensitization, most likely through PAR-2 signaling. Accordingly, pharmacological TRPV1 intervention and mast cell stabilization appears to be a valuable therapeutic approach to itching associated to hepatic disease.

FC15

THE PRURITUS OF CHOLESTASIS

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Pruritus is associated with cholestasis, impaired secretion of bile, a complication of liver disease. It is inferred that the pruritogen(s) or its cofactor(s) is made in the liver and excreted in bile, and that it accumulates in tissues as a result of cholestasis. Increased central opioidergic neurotransmission contributes to the pathogenesis of cholestasis, and mediates, at least in part, the pruritus, as supported by results from controlled clinical trials demonstrating relief of the pruritus by opiate antagonists, a therapeutic alternative. Other treatments include cholestyramine, rifampicin, sertraline, and removal of substances from the circulation by special dialysis methods. Kappa agonists, which prevent mu opioid receptor mediated scratching, are being considered to treat patients with pruritus from cholestasis. Bile acids, which accumulate in tissues in cholestasis, were reported to mediate scratching behavior in mice by mechanisms that involved gastrin releasing peptide, TGR5, and the mu opioid receptor; the relevance of these findings in cholestasis is unknown. Changes in the serum activity of autotaxin in relation with decrease or increase of pruritus in patients with liver disease may reflect changes in the degree of cholestasis, and do not confirm a role of this enzymatic pathway in the mediation of the pruritus, as proposed.

BASIC RESEARCH TRACK: ANIMAL MODELS: RODENTS, CANINES AND PRIMATES

FC16

β-ALANINE ACTIVATES UNMYELINATED NOCICEPTIVE AFFERENTS IN NON HUMAN PRIMATE

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Cutaneous polymodal nociceptive C fibers either respond quickly (QC) or slowly (SC) when stimulated with a stepped heat stimulus (49°C, 3s). QC afferents exhibit their peak discharge during the rising phase of the stepped heat stimulus, whereas in SCs, the peak discharge occurs in the plateau of the stimulus. Because QCs and SCs also respond differently to cowhage spicules we sought to determine if the responses to other pruritic stimuli also differ. β-alanine (ALA) activates C fibers in mice and produces itch sensation in humans. We therefore tested the effect of ALA on polymodal C fibers innervating the hairy skin in anaesthetized non human primates using standard teased fiber techniques. After assessing the heat response, receptive fields of afferent fibers were injected with extracellular fluid (10 µl), histamine (10 µg), and ALA (90 µg). QCs and SCs did not differ in their response to extracellular fluid or histamine. In contrast, ALA evoked a significantly greater response in QC than in SCs. These results indicate that QC fibers are more sensitive to ALA than SC fibers, and that QCs may encode the itch induced by ALA.

FC17

TRPA1 CONTROLS INFLAMMATION AND PRURITOGEN RESPONSES IN ALLERGIC CONTACT DERMATITIS

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Allergic contact dermatitis is a common skin disease associated with inflammation and persistent pruritus. Transient Receptor Potential (TRP) ion channels in skin-innervating sensory neurons mediate acute inflammatory and pruritic responses following exogenous stimulation, and may contribute to allergic responses. Genetic ablation or pharmacological inhibition of TRPA1, but not TRPV1, inhibited skin edema, keratinocyte hyperplasia, nerve growth, leukocyte infiltration and antihistamine-resistant scratching behavior in mice exposed to the haptens, oxazolone and urushiol, the contact allergen of poison ivy. Hapten-challenged skin of TRPA1-deficient mice contained diminished levels of inflammatory cytokines, nerve growth factor and endogenous pruritogens such as Substance P (SP) and serotonin. TRPA1-deficient sensory neurons were defective in SP signaling, and SP-induced scratching behavior was abolished in Trpa1-/- mice. SP receptor antagonists such as aprepitant inhibited both hapten-induced cutaneous inflammation and scratching behavior. These findings support a central role for TRPA1 and SP in the integration of immune and neuronal mechanisms leading to chronic inflammatory responses and pruritus associated with contact dermatitis.

FC18

PHARMACOLOGICAL CHARACTERIZATION OF A SURGICALLY INDUCED MOUSE MODEL OF CHOLESTATIC PRURITUS

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Patients with cholestatic liver diseases such as primary biliary cirrhosis complain of pruritus. However, the pathogenesis of and the effective treatment for cholestatic pruritus are unknown. We have developed a mouse model of cholestatic pruritus. The bile duct of the ICR mice was ligated to block bile secretion from the anterior, right, and left lobes leaving the bile secretion form the caudate lobe intact. Serum levels of total bile acids, alkaline phosphatase, GOT and GPT increased 1 week after bile duct ligationand recovered to the levels of sham-operated group at 6 weeks. Histopathological analysis revealed the fibrosis and the neogenesis of small bile ducts in the bile secretion-obstructed lobes 6 weeks after ligation. Spontaneous scratching by the hind-paws was similar between the bile-duct-ligated and sham-operated groups until 4 weeks after ligation but increased from 5 to 9 weeks. Spontaneous scratching was inhibited by naloxone (mu-opioid receptor antagonist), U-50488 (kappa-opioid receptor agonist), ondansetron (5-HT3 receptor antagonist), azelastine (H1 receptor antagonist with membrane-stabilizing activity), and proteinase-activated receptor 2-neutrolizing-antibody. Terfenadine (H1 receptor antagonist) and methysergide (5-HT2 receptor antagonist) did not inhibit spontaneous scratching. These results suggest that partial obstruction of bile secretion in mice induces itching, which is H1 antagonist resistant.

FC19

INVOLVEMENT OF OXIDATIVE STRESS IN HERPES-ASSOCIATED ITCH AND PAIN IN MICE

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We investigated the mechanisms of herpes-associated itch and pain in mice. Transdermal inoculation of human herpesvirus 1 on the mid-flank caused scratching and licking of the skin with herpes zoster-like lesions. Systemic administration of naloxone and morphine selectively inhibited the scratching and licking, respectively, suggesting that the scratching and licking are itch- and pain-related behaviors, respectively. Ablation of spinal neurons expressing BB2 bombesin receptor by intrathecal treatment with a bombesin-saporin conjugate decreased the herpes-associated scratching without effect on the licking, suggesting that BB2 receptor-expressing dorsal horn neurons play a key role in the spinal transmission of herpes-associated itch, but not pain. Systemic administration of the anti-oxidant N-acetyl-L-cysteine or the transient receptor potential ankyrin 1 (TRPA1) antagonist HC-030031 inhibited both herpes-associated scratching and licking. Hydrogen peroxide (H2O2) increased in the affected skin. Intradermal injection of hydrogen peroxide into the mid-flank elicited scratching and licking, which were also inhibited by N-acetyl-L-cysteine

and HC-030031. These results suggest that oxidative stress in the affected skin contributes to herpetic itch and pain through the activation of TRPA1 receptors. It is suggested that herpes-associated itch and pain are elicited by the same endogenous stimulus but processed by separate dorsal horn neurons.

NEUROPATHIC ITCH SYNDROMES

FC20

A CAPSAICIN 8% PATCH FOR THE TREATMENT OF BRACHIORADIAL PRURITUS

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Brachioradial pruritus (BRP) is a neuropathic localized itch at the dermatome C6. Though BRP is caused by pathological changes of the cervical spine the skin is involved, too, as reduced nerve fiber numbers have been demonstrated. We treated 7 patients (2 males, 5 females; age 60.71 (SD±5.54) years) with BRP confirmed by detectable MRT changes with the novel capsaicin 8% patch for 60 minutes under highly controlled conditions. 6/7 patients had a reduced intraepidermal nerve fiber density. Patients completed several questionnaires (Dermatology Life Quality Index questionnaire (DLQI), hospital anxiety and depression scale (HADS)). Intensity of pruritus was assessed by the visual analog scale (VAS, range 0 to 10). All patients responded of the treatment. The mean value of pruritus intensity was significantly reduced from 6.5 VAS points (SD±1.6) before treatment to 1.3 VAS points (SD±1.1) three weeks after treatment ($p<0.001$). DLQI scores reduced from 12.0 (SD±8.2) to 5.3 (SD±4.4) ($p=0.05$). HADS-anxiety score decreased from 8.9 (SD±3.6) to 6.6 (SD±2.7) ($p=0.15$); HADS-depressions score from 9.1 (SD±2.2) to 6.6 (SD±1.7) ($p=0.02$). The high response rate suggests that capsaicin 8% patch may present a novel, effective treatment strategy in BRP.

FC21

THE IMPACT OF CAPSAZEPINE ON ARTEMIN-INDUCED THERMAL HYPERALGESIA

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Previously, we reported the role of artemin in skin by confirming an effect of artemin-administration on elongation of the peripheral nerve fibers, and on thermal susceptibility of skin. However, the mechanism for artemin-induced thermal hyperalgesia remains unclear. It may be supposed that TRPV1 might involve in artemin-induced thermal hyperalgesia. To investigate the relationship between artemin and TRPV1, cultured dorsal root ganglion (DRG) cell was co-incubated with artemin *in vitro*. PCR analysis revealed the increased expression of TRPV1-mRNA in artemin-treated DRG cell. Moreover, peripheral nerve fibers in artemin-injected skin showed intense staining for TRPV1. Our previous findings confirmed that artemin-treated mice show curious behavior similar to heat-provoked scratching in warm circumstances. To investigate the involvement of TRPV1 in artemin-induced curious behavior in warm circumstances, capsazepine, a selective TRPV1-inhibitor, was administered was administered intraperitoneally. As a result, capsazepine did not affect the artemin-induced abnormal behavior. These results indicated that TRPV1 might not be involved in artemin-induced abnormal behavior, in spite of its increased expression in peripheral nervous system of artemin-injected mice.

FC22

PLACEBO EFFECTS ON ITCH: A REVIEW OF CLINICAL TRIALS

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Placebo effects have been shown to contribute to treatment effects of various symptoms and conditions, particularly pain. Numerous review articles described the role of placebo effects on pain and analgesic effects in patients as elicited in clinical trials. With respect to itch, studies investigating the placebo effect are limited. In a recent study, our research group has shown that placebo effects on itch can be experimentally induced. However, the magnitude of placebo effects on itch in the clinical setting has not been reviewed yet. To investigate the role of placebo effects on itch in clinical trials, databases of PubMed, PsychINFO and Cochrane were systematically searched for clinical studies investigating the effects of a systemic treatment on itch in patients with chronic skin conditions, in which also a placebo control condition was included. Results of this review study will be presented, providing, for the first time, indications about the magnitude of the placebo effect on itch in the clinical setting.

FC23

A PILOT STUDY OF EFFICACY OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS) OF THE MOTOR CORTEX ON NEUROPATHIC ITCH

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Transcranial magnetic stimulation (TMS) is a noninvasive method for triggering cortical action potentials from outside the scalp. Currently FDA-approved for treatment-resistant depression, repetitive TMS (rTMS) is being investigated for various neurological problems including neuropathic pain. The aim of this pilot study is to preliminarily assess motor-cortex rTMS efficacy for neuropathic itch. TMS has not previously been investigated in any itch condition. Three patients (2 men, 1 woman) with dermatomal neuropathic itch for 2–15 years provided informed consent. Two had facial postherpetic itch and one had shoulder and arm itch after spinal cord cavernous hemangioma; all had colocalizing neuropathic pain. Itch severity was measured before, during and after five consecutive days of rTMS administered to the motor cortex with Nexstim's MRI-navigated system. 10 Hz trains totaling two thousand stimuli were administered to the primary motor-cortex representation of the itchy area. Median baseline itch severity was 5/10 (range 4–10). Two patients had maximal itch reductions of 70% and 40%; both maintained 20% improvement for ≥7 days after treatment cessation. The third had no benefit and no subjects had adverse effects. These preliminary data, along with trials

demonstrating efficacy for neuropathic pain, justify a full trial of rTMS for neuropathic itch, now underway.

ITCH CLINICS

FC24

STUDY OF THE AQUAGENIC PRURITUS IN PATIENTS SUFFERING FROM MYELOPROLIFERATIVE DISORDERS

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Aquagenic pruritus (AP) is an intense prickling and stinging sensation, induced after contact with water, without any visible skin change. It is sometimes accompanied by mental symptoms (irritability, agitation) and alters dramatically the quality of life. AP is reported by 30-60% of patients suffering from a myeloproliferative disorder (MPD), the polycythemia vera (PV), but some cases exists in patients with essential thrombocythemia (ET) or myelofibrosis (MF). Etiological treatments can sometimes relief pruritus, and current symptomatic treatments are not or poorly efficient. Its pathophysiology is still unknown as well as the reasons why it disappears in some patients during treatment and not for others. We conducted a prospective study (questionnaire) validated by the regional ethics committee on 70 MPD patients (PV, ET or MF) who reported suffering from AP at some point of their hemopathy and not suffering anymore or still suffering. The main objective was to make an inventory of the occurrence, duration and treatment(s) of AP. Secondary objectives were: know the management of each patient to treat AP, determine the real impact of their etiologic treatment on AP, and determine if we have a single symptom whatever the MPD or several kinds depending on MPD. First results are presented.

FC25

PRURITUS IN PSORIASIS: AN UNDERAPPRECIATED ASPECT OF THE DISEASE WITH SIGNIFICANT UNMET NEED FOR TARGETED THERAPIES

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Pruritus is an underappreciated symptom of psoriasis. Few clinical trials have assessed pruritus and indeed pruritus is not a part of validated psoriasis scoring indices. There are no licensed medicines and treatment is focused on treating the inflammatory component of psoriasis. Recent epidemiological studies have highlighted pruritus as a significant unmet need. Pruritus affects 85% of psoriatic patients, and was the most important and severe symptom. There are significant effects on quality of life. 50% of patients report sleeping difficulties, and psychosocial effects (depression, stigmatisation) have also been associated with pruritus. 45% of patients found no treatment relieves their pruritus. We report a study of 160 psoriasis patients with mild or worse psoriasis according to an Investigator Global Assessment scale. These patients had a mean mPASI score of 8.9 and mean body surface area involvement of 6.8%. Almost all patients (97.5%) had pruritus; 68.8% had at least moderate pruritus and 33.8% had severe pruritus. We report no evidence of correlation between pruritus VAS and mPASI severity (r=0.2, r^2=3.8%). This lack of correlation suggests that treating pruritus with anti-inflammatories is a sub-optimal approach. This, and the high prevalence and unmet need, point to a need for new targeted anti-pruritic therapies.

FC26

UNEQUAL BURDEN OF DISEASES, UNEQUAL PARTICIPATION IN CLINICAL TRIALS: BISEXUAL MEMBERS IN CHITTAGONG DISTRICT OF BANGLADESH

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Due to strong belief in traditional system of medicine, Bisexual members still prefers to use traditional medicines prescribed by the Bisexual members. The studies aimed to highlight the new or lesser known medicinal uses of plants along with validation of traditional knowledge that is widely used by the Bisexual members to cure for various ailments. An open-ended semi-structured questionnaire was used in collecting field information. Descriptive statistics were used to analyze the ethnopharmacological data collected. First-hand information about 55 plants were recorded which are therapeutically used against different diseases such as rheumatism, itch problems, liver diseases, and sexual disorders. Maximum use of plants is reported to cure itch disorders 24 followed by rheumatism 17, liver problems 14, and sexual ailments 10. Most of these formulations were prescribed in powder form, whereas juice and decoction forms were also used. Since the Bisexual members of Chittagong district in Bangladesh mostly does not have access to primary medical facilities, the plants can form the basis of treatment for above diseases without resorting to costly allopathic medicine practitioner's visits. It is expected that gathering of the traditional medicinal information can lead to further scientific studies and discovery of newer drugs.

BASIC RESEARCH TRACK: NEUROIMAGING AND NEUROIMMUNOLOGY

FC27

EFFECTS OF PRURITIGENS ON ACUTE ITCH IN TRPV1/TRPA1/TRPM8 KNOCKOUT MICE

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TRP channels are known to be important regulators of itch and pain. The role of TRPV1 in histamine-induced itch was shown with a TRPV1 knockout mouse. Here we use a triple knockout model (TRPA1/TRPV1/TRPM8 -/-) to investigate role of TRP channels in the itch transmission pathway in more detail. We used the LaMotte check model to investigate the pruritic effects of histamine, serotonin, endothelin-1 and chloroquine in triple TRP KO mice. Itch responses were reduced in triple TRP KO mice to histamine, serotonin and endothelin-1. No differences with respect to scratching differences were found in littermate controls. Interestingly,

electrophysiology studies using DRG cells from triple TRP KO mice showed increased histamine-induced cell signaling for Ca^{2+}. Our results also show a gender-specific finding of chloroquine-induced scratching behavior with significantly higher scratching bouts for triple TRP KO males over females. The triple knockout mouse model is a very valuable tool to identify and decode pruritic pathways, including the chloroquine-induced itch pathway.

FC28

NEUROIMAGING AND BEHAVIOURAL EVIDENCE FOR INSULAR-MEDIATED SHARING OF AFFECT AS THE MECHANISM UNDERLYING CONTAGIOUS ITCH

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Watching someone scratch himself can induce feelings of itchiness in the perceiver. This social contagion of itch is experienced by most healthy subjects, and even more so by patients with atopic dermatitis. There are at least two possible neural mechanisms of contagious itch. First, contagion might occur because the brain internally simulates the predicted sensory consequences of observed scratching. This account predicts strong activation in fronto-parietal mirror neuron areas during contagious itch and that the same body part that is perceived to be scratched should feel itchy in the perceiver. Alternatively, contagious itchiness may be more driven by vicarious perception of the feeling state (itchiness/unpleasantness) rather than contagion of the motor act or bodily target. This account predicts that the scratched body parts can dissociate between observed itch and felt itch. Furthermore, according to this account, observing itch-related stimuli should give rise to strong insular activations, reflecting a vicarious sharing of the unpleasantness associated with itch. The recently acquired neuroimaging and behavioural data that I will present provide good evidence for insular-mediated sharing of affect as the mechanism underlying contagious itch.

FC29

GENE AND PROTEINE EXPRESSION OF OPIOID RECEPTORS IN THE SKIN OF PSORIASIS PATIENTS WITH AND WITHOUT PRURITUS

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Opioid receptors (OR) are classified as one of the main targets for peripheral skin pharmacotherapy in dermatological disorders where itch sensation occurs. It's well known that μ-opioid receptor (MOR) stimulates while κ-opioid receptor (KOR) inhibits itch signals in brain and in the skin. We have undertaken analysis of gene and proteine expression for OR in skin biopsies from normal and lesional skin of 20 psoriasis patients with and without pruritus compared to 20 healthy volunteers. Visual analoge scale (VAS) was used to evaluate pruritus intensity and psoriasis area and severity index (PASI) was employed to assess the severity of psoriasis. Relative gene expression analysis was performed for OPRM1 and OPRK1 genes in real-time PCR. OR expression was estimated by direct immunofluorescence with fluorescence intensity (FI) analysis using ImageJ. We observed downregulated expression in Ct values of OPRKI gene and FI for KOR in lesional skin compared to non-lesional and healthy skin. We showed that patients who were diagnosed with severe pruritus had significantly decreased KOR proteine expression compared to those without pruritus. Expression of OPRM1/MOR was constant in all analyzed groups. We did not observe any correlation of PASI with OR gene and proteine expression in patients with and without pruritus.

FC30

FUNCTIONAL CONNECTIVITY DURING THE CEREBRAL PROCESSING OF EXPERIMENTAL ITCH COMPARED TO PAIN

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Several fMRI studies have revealed that experimental itch and pain are processed in largely overlapping cerebral networks involving cortical somatosensory areas, insular cortices, frontal areas, limbic structures, thalamus and basal ganglia. Here we explored the functional connectivity within these brain regions during tonic itch and pain. Tonic pain which was induced by squeezing an inter-digital web of the left hand three times for two minutes. Itch was induced by iontophoretic application of histamine. Standard fMRI sequences were used to record cortical BOLD signals. BOLD time courses obtained during the stimulations were extracted from brain regions of interest (ROI) and were correlated to selected seed areas. Functional connectivity was more pronounced during pain than during itch, in particular in the lateral projection system and thalamus. Less synchronicity was found between regions of the lateral system and the medial system or frontal areas, respectively, during both stimulation conditions. Higher functional connectivity during pain may indicate higher synchronized activity of neuronal assemblies during pain, probably involving larger neuronal populations. Interestingly, the regions revealing the highest correlations were similar in the pain and itch state. These results confirm the processing of itch and pain in closely related networks.

FC31

THE ION CHANNEL TRPA1 IS REQUIRED FOR CHRONIC ITCH

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Chronic itch is a debilitating condition that affects one in ten people. Little is known about the molecules that mediate chronic itch in primary sensory neurons and skin. We demonstrate that the ion channel TRPA1 is required for chronic itch. Using a mouse model of chronic itch, we show that scratching evoked by impaired skin barrier is abolished in TRPA1-deficient animals. This model recapitulates many of the pathophysiological hallmarks of chronic itch that are observed in prevalent human diseases such as atopic dermatitis and psoriasis, including robust scratching,

extensive epidermal hyperplasia, and dramatic changes in gene expression in sensory neurons and skin. Remarkably, TRPA1 is required for both transduction of chronic itch signals to the CNS and for the dramatic skin changes triggered by dry skin-evoked itch and scratching. These data suggest that TRPA1 regulates both itch transduction and pathophysiological changes in the skin that promote chronic itch.

FC32

BRAIN CIRCUITRY SUPPORTING NOCEBO ITCH PERCEPTION IN ATOPIC DERMATITIS

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Psychogenic factors are known to significantly modulate itch in atopic dermatitis (AD). Itch is susceptible to both placebo and nocebo effects. We evaluated 14 AD patients (25.4±9.1 years old, SCORAD: 38.7±14.9). Functional MRI data were collected while subjects were stimulated with our allergen temperature-modulated itch model. Different scans were performed with (1) subject-specific allergen skin prick, (2) open saline skin prick, where subjects were informed of saline, (3) hidden saline skin prick, where subjects were not informed and assumed allergen stimulation (nocebo condition). Hidden saline produced greater itch sensation than open saline (hidden: 36.9±21.2; open: 18.5±18.6, $p<0.05$). FMRI data showed that compared to open saline, brain response to hidden saline showed greater activation in caudate, dorsolateral PFC (dlPFC), and posterior parietal cortex. Real allergen produced activation in similar areas, including the striatum and dlPFC. Brain response to real allergen in these regions was correlated with the difference between brain response to hidden versus open saline - i.e. subjects with greater dlPFC activation to allergen also had greater dlPFC activation to hidden saline. Our results suggest that when subjects perceive nocebo induced itch, the prefrontal and striatal circuitry activated by real allergen is also activated to support this sensation.

FC33

NEURAL RECRUITMENT AND ACTIVITY IS INTEGRAL TO THE PATHOGENESIS OF ATOPIC DERMATITIS

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Atopic dermatitis (AD) is a common, frequently disabling disorder characterized by pruritus and inflammation. In addition to barrier dysfunction and immune dysregulation, alterations in neural innervation and neurogenic inflammation play important roles in AD pathogenesis. In this study, we characterize changes in neural innervation in eczematous skin and determine when changes in sensory innervation patterns occur. We performed *in vivo* confocal imaging of fluorescently-labeled peripheral sensory nerves in mice during epicutaneous sensitization (ECS) to ovalbumin, an allergic mouse model of AD. Visualization of the same cutaneous nerves over time revealed that specific subpopulations of peripheral sensory nerves are highly dynamic throughout eczema development, eventually resulting in higher innervation density and arbor complexity. Neural sprouting occurred early in the evolution of the dermatitis, within days of ovalbumin sensitization. Increases in the total number of nerve branches expressing substance P and calcitonin gene-related peptide were observed in ovalbumin-treated skin compared to saline-treated controls. Neural changes were independent of scratching behavior. Neural blockade during weeks of ECS prevented ovalbumin-induced neural pattern changes and reduced scratching behavior. Our results suggest that cutaneous inflammation promotes re-organization of sensory innervation patterns early in AD pathogenesis and that different neural populations contribute to the development of eczema.

CLINICAL RESEARCH TRACK: METHODOLOGY FOR CLINICAL RESEARCH IN ITCH

FC34

ASSOCIATION BETWEEN ITCH, STRESS AND COPING IN PATIENTS WITH ATOPIC DERMATITIS

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Aim: In patients with atopic dermatitis (AD) itch and self-rated stress are related. However, it is unclear, whether physiological stress markers and disease specific coping strategies are also associated with itch in AD-patients. Thus, we investigated the relationship between itch intensity, self-rated stress, coping and the cortisol-awakening-response (CAR) as a marker of chronic stress in AD-patients. *Methods*: The CAR was determined in 31 AD-patients (22 females; 9 males) on two consecutive days. The mean of both days was calculated in order to minimize error variance. On day 2, psychological stress and disease specific coping were measured by validated questionnaires. Itch intensity was determined in the context of assessing the SCORAD. *Results*: Self-rated stress and itch were highly correlated ($r=0.529$; $p=0.002$), while the CAR was not significantly associated with itch ($r=0.102$; $p=0.593$). Additionally, five out of six scales measuring disease specific coping were significantly associated with itch (all $r\geq0.403$; all $p\leq0.025$). *Conclusions*: This study showed that itch is significantly associated with self-rated stress and coping strategies in AD-patients. In contrast, there was no significant association between itch and the CAR in this patient group.

FC35

THE PREVALENCE AND INTENSITY OF ITCH AMONG DERMATOLOGICAL PATIENTS IN 13 EUROPEAN COUNTRIES

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Introduction: Itch is the most common symptom in patients with dermatological disease. Objectives To describe the prevalence and

intensity of the symptom itch among dermatological patients in 13 European countries. Material and Methods: In dermatological clinics in 13 countries in Europe, a questionnaire was filled in by 250 consecutive patients. In addition 125 healthy controls filled in a questionnaire in each country. The questionnaire had an item on the presence of itch or not, and if yes the duration and intensity of itch assessed with a visual analogue scale. The study was approved by the Ethical Committee of Oslo and from each participating country. The diagnoses were categorized in 26 groups of common skin conditions. *Results*: The total number of responders was 4994 (3635 patients and 1359 controls). The prevalence of itch was 54.4% in patients and 8% in controls. The intensity (range 0–10) was highest in patients with prurigo (7.4±2.3), lowest in patients with non melanoma skin cancer (4.0±2.4) and benign skin tumors (4.0±2.0). *Conclusions*: The presence and intensity of itch varies among different skin diseases and is common symptom among the controls. The findings underline the importance of developing new treatment modalities for itch.

FC36

CARPE - NEW RESULTS ON ITCHING IN PATIENTS WITH CHRONIC HAND ECZEMA

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The German CARPE Registry was established to better understand characteristics and treatment modalities in patients suffering from chronic hand eczema (CHE). CARPE prospectively assesses patients with CHE by means of dermatological examinations and patient questionnaires. Itching in relationship with diagnosis, systemic therapy and severity of CHE was investigated. Severity of itch was evaluated by a physician in four categories (none, moderate, average, severe). 1201 patients were included in the analysis; from those 81.7% reported itching, 19.3% of CHE-patients were not affected by itch. Most patients were diagnosed with an irritant contact dermatitis (45.5%). Regarding itch, the most dominant eczema-diagnosis was allergic contact dermatitis: 90.5% of patients with this diagnosis reported itching and were more likely to experience itch compared to patients with other diagnosis [OR= 2.7; 95% CI: 1.74; 4.19]. Systemic treatment was significantly associated (p=0.01) with itch. 26.9% of patients with systemic treatment were affected by severe itch, compared to 19.8% of patients without systemic treatment. 75.9% of patients with itch were affected by a very severe or severe form of CHE. These data show that itch is a dominant and important symptom in patients with chronic hand eczema and is associated with type of treatment.

FC37

COMPARISON OF VISUAL ANALOGUE SCALE AND VERBAL RATING SCALE IN JAPANESE PATIENTS

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Pruritus is a subjective complex symptom that cannot be precisely measured in a objective way. However, there have been established several methods to estimate the intensity of pruritus. Herein, we assessed the relationship between Visual Analogue Scale (VAS) and Verbal Rating Scale (VRS) in 949 Japanese patients with skin diseases in 4 University Hospitals to find out the reproducibility of these scores in comparison with previous reports of different ethnic group and analyzed factors influencing VAS or VRS scores. VAS significantly correlated with VRS (R=0.94, p<0.001). Each category of VRS differed significantly from the others regarding the VAS scoring (p<0.001). Cut-off value (3–7–9), 0<mild<3, 3≥moderate<7, 7≥severe<9, and ≥9very severe, was the most suitable set of bands for VAS, which was consistent with the previous report in Caucasian (Reich et al., 2012). There was some regional difference in the expression of itch intensity in Japanese patients (p<0.05). These results indicate that VAS and VRS are valuable reproducible methods for pruritus evaluation, irrespectively of ethnic difference. We should keep in mind, however, that these score might be influenced by some factors including regional difference.

NEW TREATMENTS

FC38

TOPICAL VITAMIN D3 THERAPY FOR STEROID RESISTANT PRURIGO: ANTI-INFLAMMATORY ACTION OR NEUROPROTECTIVE EFFECT

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New role of vitamin D3 has been discussed on modulation of innate immunity and allergic inflammation including atopic dermatitis. *Objective*: We have previously reported that topical vitamin D3 improved steroid-resistant refractory prurigo. In the case of responder group, pruritic sensation was reduced soon after the start of vitamin D3 with reduction of scratching behavior. However, mechanism of action of vitamin D3 to pruritic skin disease remains unclear. *Method*. Immuno-histochemical analysis on prurigo after topical vitamin D3 therapy was performed. Effect of vitamin D3 [1alpha,24(R)-dihydroxyvitamin D3] on chemokines and NGF productions by cultured normal human keratinocytes (KC) and fibroblast (FB) was analysed. *Result*. *In vitro* studies demonstrated that vitamin D3 down-regulates CXCL1, TNFα, RANTES production from KC and surprisingly up-regulates both mRNA expression and protein of NGF by cultured KCs. In addition vitamin D3 suppressed eotaxin production from FB derived from prurigo (Prurigo fibroblast) but not normal skin. *Conclusion*: Vitamin D3 might be useful for refractory prurigo through possible restoration of injured peripheral nerves elongated into epidermis and inhibition of chemokine production from prurigo-derived fibroblast.

FC39

COWHAGE-INDUCED PRURITUS: FURTHER VALIDATION OF AN EXPERIMENTAL ITCH MODEL

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To develop novel therapies for itch, experimental models in humans are needed. Here, we characterized an itch model using cowhage. First, we assessed in 20 healthy volunteers effects after skin provocation with histamine or cowhage by volumetry, thermography and erythema, TEWL, and itch intensity and duration. Histamine- but not cowhage-induced pruritus was associated with an induction of skin inflammation as measured by volumetry, thermography and erythema. Mean itch intensity over time and maximum itch intensity after cowhage provocation were comparable to histamine. Most interestingly, itch was significantly lower in a second application of cowhage 30 minutes after a previous, contralateral provocation. Based on these findings, we used the developed standardized experimental itch model in a double-blind, randomized therapeutic application of polidocanol 3% solution vs. placebo in 45 volunteers. We detected a significant reduction of maximum itch intensity (31.6±4.8 vs. 21.2±3.5 [VAS], $p<0.05$) and mean itch intensity over time 254.6±56.7 vs. 111.0±20.4 [AUC of VAS], $p<0.05$) as compared to placebo control. Here, we describe the development of a standardized model of experimental non-histamine-mediated pruritus in healthy volunteers. We confirmed the validity of the cowhage-induced itch model in a randomized, placebo-controlled study, showing a significant anti-pruritic effect of 3% polidocanol vs. placebo.

FC40

NALFURAFINE FOR TREATMENT OF UREMIC PRURITUS IN SUBJECTS WITH END-STAGE RENAL DISEASE RECEIVING HEMODIALYSIS

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Nalfurafine was first described 15 years ago as a potent, centrally active kappa opioid agonist. Potent, dose-related anti-scratch activity was revealed in mouse assays using histamine-dependent and histamine-independent pruritogens. Additionally, nalfurafine inhibited c-fos expression induced by GNTI and compound 48/80 in the dorsal horn of the mouse spinal cord, suggesting inhibitory activity at the spinal level. On the basis of these preclinical studies, nalfurafine held promise as a potentially useful, first in class, antipruritic in human conditions involving itch. In 2009, nalfurafine received Japanese approval for the treatment of uremic pruritus (UP). UP is a chronic pruritic disorder of systemic origin which occurs in 70% of patients receiving chronic hemodialysis and is associated with increased morbidity, mortality, and impaired quality of life (QoL). Despite medical need, there is no approved treatment in North America. Nalfurafine is currently being investigated in the US and Canada as a once daily oral therapy for UP in chronic hemodialysis patients. 360 subjects from 90 centers will be randomized equally into 1 of 4 double-blind treatments (2.5, 5, or 10 μg nalfurafine or placebo) in this Phase 2 study, which features an 8-week active treatment phase. Efficacy, safety, QoL, and pharmacokinetics will be evaluated.

FC41

HISTAMINE H4 RECEPTOR ANTAGONISTS INEFFECTIVE AGAINST ITCH AND SKIN INFLAMMATION IN ATOPIC DERMATITIS MOUSE MODEL

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Histamine H1 receptor (H1R) antagonists are commonly used to treat patients with atopic dermatitis (AD). However, the treatment is usually ineffective against chronic pruritus. Recent studies using mouse model of pruritus have demonstrated that histamine H4 receptor (H4R) is also involved in histamine-dependent itch. We examined the efficacy of two H4R antagonists, JNJ7777120 and JNJ28307474, as treatments for itch and skin inflammation in NC/Nga mice, which is a model for AD. AD-like symptoms were induced in NC/Nga mice by repeated application of Dermatophagoides farinae body (Dfb) ointment. Mice that scored over 5 on the scoring system for dermatitis severity were treated by either intraperitoneal injection with control vehicle or the H4R antagonists (10 mg kg-1 or 30 mg kg-1) 3 times per week for 3 weeks. Neither of these H4R antagonists showed significant amelioration of dermatitis nor inhibited scratching behaviour. Moreover, the number of scratching bouts significantly increased by treatment with 30 mg kg^{-1} JNJ28307474. There was no significant difference in locomotion activity among treated-mice and controls. Accordingly, these H4R antagonists are insufficient to treat itch and skin inflammation in Dfb ointment-induced AD mouse model.

FC42

AN H4R ANTAGONIST, JNJ-39758979, IS EFFICACIOUS IN CLINICAL STUDIES OF EXPERIMENTAL ITCH AND ON ITCH IN ATOPIC DERMATITIS

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JNJ-39758979 is a potent oral H4R antagonist that has efficacy in preclinical models of itch. To explore the role for the H4R in itch in humans, the effects of JNJ-39758979 on itch was assessed in two clinical studies. The first study evaluated the effect and safety of single oral dose of JNJ-39758979 on histamine-induced pruritus in healthy male subjects with cetirizine used as a positive control. Treatment with JNJ-39758979 demonstrated a significant decrease in pruritus 2 and 6 hours post-dose when compared with placebo. The second study assessed the safety and efficacy of JNJ-39758979 in patients with moderate atopic dermatitis. Although the primary endpoint (Δwk 0−6 in Eczema Area and Severity Index score) was not significant, nominally significant symptomatic improvement was seen in patient-reported itch severity and duration. However, the study was terminated prematurely due to agranulocytosis reported by two patients who received JNJ-39758979. Both patients recovered 1−2 wks after stopping dosing. Further investigations suggested that the cause of agranulocytosis is due to off-target effects of JNJ-39758979 or its metabolites, and not the effects of H4R antagonism. The clinical data suggest that H4R antagonism may be beneficial in control itch in atopic dermatitis and other pruritic indications.

ABSTRACTS: Poster Presentations (101–168)

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ANALYSIS OF STRATUM CORNEUM LIPID COMPOSITION IN RELATIONSHIP TO UREMIC PRURITUS

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The aim of the study was to analyse the lipid composition of the stratum corneum in patients undergoing haemodialysis and to evaluate its influence on the perception of uremic pruritus. 80 patients on haemodialysis (30 females and 50 males) in the age between 25 and 90 years (mean 59.9±15.6 years) were compared with 32 healthy volunteers (19 females and 13 males) in the age between 22 and 86 years (mean 59.7±16.0 years). Lipids were isolated from epidermal scrapings using a two-step chloroform/methanol/water extraction and assessed according to the 3-step thin layer chromatography (TLC). The content of identified lipid classes was demonstrated as a percentage of the total lipids isolated. In addition, transepidermal water loss (TEWL), electric impedance of the stratum corneum, xerosis severity and intensity of pruritus using Visual Analogue Scale and the 4-point Itch Questionnaire were evaluated in each subject. Haemodialysis patients showed significantly decreased levels of cholesterol (22.5±8.0% vs. 28.5±9.7%, p=0.001) and triacylglycerols (6.5±5.8% vs. 10.5±6.4%, p=0.002) in stratum corneum, while ceramides were markedly increased (33.4±8.7% vs. 25.1±9.5%, p<0.001). However, no relationships between epidermal lipid composition and the degree of xerosis as well as the presence and intensity of pruritus were observed.

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REDUCED INTRAEPIDERMAL NERVE FIBRE DENSITY IN PRURIGO NODULARIS OF DIFFERENT STAGES

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A reduced intraepidermal nerve fiber density (IENFD) was demonstrated in prurigo nodularis (PN). In order to characterize the IENFD in different PN stages, biopsies of nodules (lesional), interlesional skin, healed nodules and nonlesional skin of PN patients were compared. Biopsies from 25 patients (19 women, 6 men, average age 58.2 ± 15.2 years) with PN of different origin were immunostained for PGP 9.5 and analyzed according to a counting Guideline (normal value, >9 fibers/mm). Lesional PN biopsies (7.21±6.01 fibers/mm) showed significant decreased IENFD in comparison with nonlesional (11.39±7.79; p=0.035) and healed skin (12.73±6.56; p=0.011) regardless of age, intensity or quality of pruritus. The difference between interlesional skin (7.83±6.68) and either healed (p=0.018) or nonlesional skin (p=0.007) was significant, too. The lesional IENFD was significantly higher in women (8.58±6.05) than in men (3.09±3.85, p=0.027). IENFD was highest at the trunk (11.17±6.5), followed by arms (7.38±5.14) and legs (3.07±3.53). Difference between IENFD at trunk and legs (p=0.010) and at arms and legs (p=0.046) was significant. Our results confirm that hypoplasia of epidermal nerves is a specific finding in PN and normalizes during healing. This suggests that reduced IENFD is an important finding in PN that most likely contributes to pruritus induction.

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ALTERED CUTANEOUS INNERVATION IN PRURITIC DERMATOSES.

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Growing evidence suggests that the ability of overlapping sensory populations to encode distinct sensations of itch and pain partially lies with distinct anatomic sites of nerve fiber termination within the skin. Human studies with cowhage, a potent pruritogen, suggest that itch-specific pathways reside along the dermo-epidermal junction (DEJ). In contrast, intraepidermal nerve fibers (IENFs) express TRPV1 and transmit noxious heat and mechanical pain. At the spinal level, nociceptive signals transmitted from IENFs may inhibit incoming pruritoceptive signals. To test the hypothesis that itch in chronic pruritic disorders arises from decreased nociceptive IENFs or increased pruritoceptive fibers at the DEJ, we performed immunohistochemistry and confocal microscopy on human tissue from lichen simplex chronicus (LSC), lichen amyloidosis (LA), and age- and sex-matched control skin using antibodies against multiple neuronal markers. We show that total TRPV1+ length is reduced in LA, but not in LSC compared to controls. PGP9.5+ nerve fiber length appeared unchanged in pruritic skin compared to controls. Peptidergic innervation was sparse and remained limited to the DEJ in LSC, LA and controls. Thus, some types of itch arise due to a loss of itch-inhibition provided by nociceptive fibers in the superficial skin layers in the setting of maintained pruritoceptive input.

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ASSESSMENT OF PRURITUS IN PATIENTS WITH SCALP PSORIASIS: CLINICAL CHARACTERISTICS AND ASSOCIATION WITH DENSITY OF INTRAEPIDERMAL NERVE FIBRES

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Background: Scalp psoriasis can be attributed not only to the cosmetic embarrassment, but pruritus which adversely affect quality of life. *Objective:* To determine the possible correlation between clinical characteristics of pruritus, the severity of scalp psoriasis (PSSI) and the density of intra-epidermal nerve fibres (IENF). *Methods*: A total of 80 patients with scalp psoriasis were enrolled for evaluation of the clinical characteristics of pruritus and PSSI. Biopsies were taken from lesional and nonlesional skin

of 19 patients. Immunofluorescence staining using protein gene product (PGP) 9.5 and confocal laser scanning microscopy were performed to determine the density of IENF. *Results*: Sixty-four (80%) patients complained of pruritus and it negatively affected quality of life in varying degree. There was a moderate positive relationship between PSSI score and intensity of pruritus (r=0.225 and p=0.044). The density of IENF in psoriatic lesion was significantly higher than that in nonlesional scalp. However, correlation between density of IENF and PSSI score, and density of IENF and intensity of pruritus were not significant. *Conclusion*: The prevalence of pruritus is significantly high among patients with scalp psoriasis and it showed considerable impact on patients' daily living and quality of life. Increased density of IENF in psoriatic scalp lesions may have a role in development of pruritus.

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TRICHOKNESIS - A FORM OF TRICHODYNIA OR A DISTINCT ENTITY?

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Trichodynia refers to pain within hair or scalp, which become more intense when hair is touched. Trichodynia is frequently considered as a form of a somatoform disorder and patients with trichodynia may present other psychiatric symptoms. Here, we would like to demonstrate a 57-year-old Caucasian male who suffered from pruritus limited to hairy skin, including scalp, eyebrows, moustache and hair of the chest. Sensation of itch has been becoming more intense when hair was touched. First symptoms of itching appeared more than 30 years ago and initially had been diagnosed as hypochondriac neurosis. The patient had been admitted to the psychiatric ward for insulin shock therapy. Next the patient was treated with promethazine, thioridazine, hydroxyzine, psychotherapy, systemic antibiotics and topical steroids without any improvement. Based on clinical appearance, a somatoform sensation was diagnosed. Per analogy to trichodynia we used a term "trichoknesis", as the touch of hair provoked marked increase of itching sensations, which is a very similar phenomenon to alloknesis, where lightly touching of normal skin near a site of itch can elicit itch sensation. Whether trichoknesis is a special form of trichodynia or is a distinct entity remains to be solved in the future.

106 Duplicate.

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EVIDENCE OF CATHEPSIN S, PAR2 AND HISTAMINE INTEREST IN PRURITUS ASPECT OF CLINICAL DANDRUFF/SEBORRHEIC DERMATITIS EVALUATION.

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Background: The dandruff pathogenesis is based on several interacting factors including fungi, skin barrier dysfunction and inflammation. Clinical descriptors are well established and give a general score of severity including flakes, erythema and pruritus. *Objective*: We have investigated the importance of skin surface biomarkers in scalp pruritus between two population, D/DS vs. healthy, and if these biomarkers could be reversed by specific treatment. *Materials and methods:* First dandruff populations with a positive Overall Clinical Score (OCS) and a normal population with null OCS were compared. Skin surface sampling was used to determine biomarkers of pruritus (histamine, proteinase-activated receptor 2 and the probably involved cathepsin S). Secondly we used these biomarkers to evaluate if a 2-week specific shampoo treatment could reverse their levels and if there were correlation between biomarkers levels and clinical descriptors. *Results*: In the validation study, the three biomarkers levels were significantly increased in D/DS. In the efficiency study, they were completely decreased after treatment. Finally, the overall efficiency, the OCS and pruritus were linked to these biomarkers. *Conclusion:* We have supplemented the list of used biomarkers to objective clinical efficiency of dandruff scalp with cathepsin S which is probably a key for understanding pruritus.

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FURTHER RESEARCH ON MENTAL ITCH INDUCTION: IS CONTROL OF SCRATCHING ASSOCIATED WITH A CERTAIN PERSONALITY STRUCTURE?

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Aim: Scratching can be induced by certain video-presentations. However, during former investigations we got the impression that some participants even scratched more often when the video presentation was stopped – maybe because they did not feel observed anymore. This study aimed to identify three groups of participants ("Controlled": no scratching during video-presentation, but thereafter; "uncontrolled": scratching during video-presentation, but not thereafter; "neutral": no change in scratching from video- presentation to thereafter) and to investigate whether these groups differed in personality characteristics. *Methods*: In 60 skin patients (18 with atopic dermatitis, 24 with psoriasis, 18 with chronic urticaria) and 35 healthy controls scratching was induced by the method of mental itch induction. Subjects were presented an itch inducing video (experimental video; EV) on skin diseases or crawling insects and a control video (CV) in counterbalanced order. After each video a 20-minute wash-out period followed, during which the participants filled in questionnaires to measure personality characteristics. *Results*: The subjects` scratch movements during the first five minutes of the video-presentations and wash-out periods have already been counted by two independent persons. The statistical analyses will be completed soon, so that the results can be presented at the congress.

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IONTOPHORESIS IS A NON-INVASIVE METHOD TO STUDY PRURITUS IN MICE

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Different approaches are used to investigate pruritogen-induced scratching behavior and acute pruritus in mice. Recently, LaMotte et al. established the cheek model: pruritogens and pain mediators are i.d. injected into the shaved skin of the cheek. Thereby the investigator has the possibility to distinguish between scratching (itch-related behavior) and whipping (pain-related behavior) in rodents. However, intradermal injection (i.d) of compounds is an invasive procedure and can induce pain-related behavior. Here, we present a further advancement of the LaMotte cheek model. We used iontophoresis to apply pruritogens (histamine, 5-HT, SLIGRL) or an algogen (bradykinin) on the shaved skin of the cheek and monitored side-specific scratching behavior in mice. After defining the polarity of the pruritogens we applied 5-HT, SLIGRL and bradykinin from the anode, and histamine from the cathode. All tested pruritogens induced scratching behavior in mice in a concentration depending fashion. Although i.d. injection of pruritogens results in a greater scratching response per 30 min as compared to iontophoresis, non-invasive iontophoresis was well reproducible, showed significant scratching responses as compared to controls, was less invasive, non-painful and highly consistent. Another advantage of using this approach is that only peripheral nerve fibers become activated and can therefore distinguish between peripheral and central pathways of acute and chronic pruritus.

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ENDOTHELIN-1-INDUCED PRURITUS IS REGULATED BY ENDOTHELIN-CONVERTING ENZYME-1 IN MICE AND HUMANS

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Pruritus, a somatosensory sensation, is a frequent symptom in numerous skin and systemic diseases with poorly understood mechanistic insights in humans. Endothelin-1 (ET-1) evokes histamine-independent pruritus in mammals by activating its G protein-coupled receptor, Endothelin A receptor (ETAR). Here, we identified neural endothelin-converting enzyme-1 (ECE-1) as a key regulator of ET-1-induced pruritus and neural signaling in itch. In murine DRG neurons, ET-1 induced internalization of ETAR to ECE-1-containing endosomes. ECE-1 inhibition decelerated ETAR recycling and prolonged ET-1-induced phosphorylation of ERK1/2 (but not p38, JNK or PKC). In mice, ET-1-induced scratching behavior was significantly augmented by ECE-1 inhibition and abrogated by ERK1/2 inhibition *in vivo*. Using iontophoresis, we highlight that ET-1 is a potent histamine-independent pruritogen in humans. Immunohistochemical results also indicate an important role of the ET-1/ETAR/ECE-1/ERK1/2 axis in patients with atopic dermatitis and prurigo nodularis. Our results indicate that a neural peptidase, ECE-1, directly regulates ET-1-induced, histamine-independent pruritus in humans and mice, and implicate the ET-1/ECE-1/ERK1/2 pathway as an important target to treat chronic pruritus in humans.

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SELECTIVE ROLE OF SPINAL GASTRIN-RELEASING PEPTIDE RECEPTOR IN REGULATION OF ITCH NEUROTRANSMISSION IN MICE

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Bombesin receptor subtypes in the spinal cord i.e. receptors for gastrin-releasing peptide (GRPr) and neuromedin B (NMBr) differentially regulate itch neurotransmission. The extent to which these receptors control scratching elicited by intrathecally administered bombesin-related peptides is unknown. In the present study, dose-response curves for scratching induced by intrathecally administered bombesin-related peptides were characterized in mice and compared with morphine. Additionally, the functions of spinal GRPr and NMBr in mediating scratching behavior were also determined. Bombesin (0.01–0.3 nmol) elicited maximum scratching over one hour followed by GRP (0.01–0.3 nmol) and NMB (0.1–1 nmol), whereas morphine (0.3–3 nmol) failed to evoke scratching response indicating the insensitivity of the mouse model to intrathecal opioid-induced itch. At functionally receptor-selective doses, intrathecal pretreatment with GRPr antagonist RC-3095 (0.03–0.1 nmol) produced a rightward shift in the dose response curve of GRP but not NMB-induced scratching. Similarly, NMBr antagonist PD168368 (1–3 nmol) attenuated NMB but not GRP-induced scratching. Individual or co-administration of antagonists failed to attenuate bombesin-evoked scratching. General suppression of scratching by a higher dose of RC-3095 (0.3 nmol), was confounded by motor impairment. Therefore, spinal GRPr seems to independently drive itch neurotransmission. The GRPr antagonist is only effective in blocking GRPr-mediated itch.

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NATUROPATHIC TREATMENT OF PRURITUS – A REVIEW

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Background: Pharmaceutical products based on herbal components are popular, due to their reputation to be safe. According to general opinion, adverse effects are rare. However, the efficacy of phytotherapeutic ointments and other products for external application must yet be approved. This study investigated the level of evidence for naturopathic treatment of pruritus. *Method*: Literature based on PubMed-listed publications was reviewed in order to evaluate evidence for the efficacy of certain phytotherapeutic medication. *Results*: The highest level of evidence for the efficacy in the treatment of pruritus was found for cayenne pepper, followed by witch-hazel and birch bark. Plant extracts derived from black tee, chamomile, marigold, balloon plant, horsetail, comfrey, oak bark, lavender oil, aloe vera, coriander, bittersweet, and evening primerose are recommended for the treatment of pruritus. However, their level of evidence concerning efficacy is low. *Conclusions*: Clinical trials are mandatory for newly introduced medication. Naturopathic treatments have been carried out for decades. In former times, clinical trials were not legally required. Therefore, there is a huge necessity for new clinical trials.

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HEALTH-RELATED QUALITY OF LIFE IN HAND ECZEMA: ITCH IS THE MOST IMPORTANT SYMPTOM

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Hand eczema (HE) can lead to long lasting impairments of health related Quality of Life (HRQOL) in those affected. Since there is no disease-specific HRQOL instrument to assess HRQOL impairments in HE patients a new Quality of Life in hand eczema questionnaire (QOLHEQ) was developed. The development process was set according to the guidelines for the development of patient reported outcomes (PROs) provided by the Food and Drug Administration. After receiving a first draft we performed expert (n=38) and patient (n=35) ratings on a numeric rating scale ("0" not important to "100" very important") on the items and discussed the QOLHEQ in focus groups with patients. We received a final draft of the QOLHEQ with 30 items covering the domains symptoms, emotions, functioning and treatment/prevention. Itch was rated as being the most important item of the symptoms scale to assess HRQOL in HE by the experts (mean: 86.7, SD 21.3) as well as by the patients (mean: 78.2, SD 17.1). The other items covering symptoms were rated by the patients as follows (mean): painful (66.6), fissuring (66.5), burning (64.2), dryness (62.9), bleeding (62.4), and redness (53.4). Those results show that itch is the major symptom in HE patients. Therefore this symptom should be considered in any HE therapy.

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EPIDEMIOLOGY OF ECZEMAS HOSPITALIZED PATIENTS YOUNGER THAN 18 IN HOSPITAL IN KINSHASA/R.D.CONGO

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Introduction: Eczema inflammatory skin diseases are the most common of childhood, characterized by a red itchy rash that usually involves the face and skin folds. The objective of this study was to estimate the prevalence of eczema in Kinshasa hospital. *Methodology*: Multicenter study documentary on patients 0 to 18 years who consulted for eczema to the department of dermatology at three private hospitals: Bondeko Clinic, Victoria Hospital and Akram Medical Center, from January 2010 to June 2012. *Results*: In these hospitals, 387 patients aged 0–18 years had consulted for all sorts of skin diseases, including 43 with eczema, a frequency of 11.1%. A female predominance was noted in 58.1% against 41.8% for males. The average age was 8.3 years, the age group 7–12 years was the most affected, a history of atopy was found in 56% of cases. 21.3% of cases had a secondary infection of the lesions. Associated diseases were essentially: allergic rhinitis (23.2%), allergic conjunctivitis (16.2%) and asthma (11.6%). *Conclusions*: The frequency of eczema in children under 18 years is 11%, the female is most affected, a history of atopy was found in more than half of the cases, 1/5 patients superinfection of lesions were found. *Key words*: Prevalence-Eczema-Kinshasa.

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RACIAL VARIATIONS IN PRURITUS SEVERITY

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Several studies report a lifetime prevalence of chronic pruritus to be over 20% of the population, but risk factors for itch and their contribution to symptom severity is not well understood. We conducted a national cross-sectional study of patients sampled from the U.S. Veterans Hospital Patient Database to further investigate these questions. 403 patients reported chronic pruritus and subsequently answered questions related to demographics, medical history, known pruritus risk factors, and itch severity. Ordinal logistic regression was performed analyzing severity of itch as the outcome variable grouped into categories: low, medium, and high, to see if any of the demographic and risk factor data were independent predictors of pruritus severity. Race was a significant predictor of pruritus severity (p=0.0004). American Indian/Alaskan Native patients (n=25) reported relatively milder pruritus symptoms, having a severity 0.402 times (CI 0.175–0.919) that of Caucasians (n=282). African-American patients (n= 74) and patients who identified their race as "other" (n=24) both reported increased pruritus severity, having severities 2.164 times (CI 1.273–3.679) and 2.612 times (CI 1.100–6.200) that of Caucasians, respectively. These results demonstrate that race is not only a risk factor for pruritus but also contributes to severity of itch.

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BREAKING THE GLASS: NAVIGATING THE STIGMA OF PAIN AND ITCH IN BANGLADESHI TRIBES AND REFUGEES

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Traditional medicinal practitioners (TMPs) form the primary health-care providers to the majority of tribes and refugees of Bangladesh. Each TMPs possess extensive knowledge of plants and usually has his own formulations for treatment of various ailments. Since itch affects a huge number of people worldwide, including Bangladesh, we conducted a survey amongst the TMPs of various regions of Bangladesh to learn more about plants used to treat various forms of itch. Interviews were conducted with the help of a semi-structured questionnaire and plant specimens as pointed out by the TMPs were collected and identified at the Bangladesh National Herbarium. The plant names obtained in our survey included Abrus precatorius L., Aloe vera (L.) Burm.f., Alpinia galanga (L.) Willd., Amorphophallus konjac K.Koch, Azadirachta indica A.Juss., Barringtonia acutangula (L.) Gaertn., Borassus flabellifer L., Brassica oleracea L., Calendula officinalis L., Camellia sinensis (L.) Kuntze, Cinnamomum camphora (L.) J.Presl, Citrus sinensis (L.) Osbeck, Colocasia esculenta (L.) Schott, Curcuma longa L., Cynodon dactylon (L.) Pers., Dioscorea bulbifera L., Euphorbia antiquorum L., Ichnocarpus frutescens (L.) W.T.Aiton, Indigofera tinctoria L., Nigella sativa L., Olea europaea L., and Senna alexandrina Mill.. It is expected that scientific studies on these plants shall lead to discovery of novel anti-itch compounds.

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CONCEPTS OF DERMATOLOGY SYNDROME AND ITS HEALING AMONG RESIDENTS OF RAJBARI DISTRICT BANGLADESH: PRECLINICAL EPIDEMIOLOGY STUDIES

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Plant based drugs have received more attention in research and product development in resent time. Dermatology syndrome is a common problem since ancient time but presently in the modern era of fast life and junk food it is increasing very much. The work is in the form of inventory which includes information on plants useful against dermatology syndrome in human-beings as studied from the Rajbari district of Bangladesh. Periodic field trips were organized in connection to different seasons during the year July 2010–June 2013 in different parts of Rajbari district. The plants mentioned were authentically identified and their herbarium specimens are maintained in the Bangladesh National Herbarium for future reference and studies. Total of 18 plants were reported by the local practitioners for the treatment of dermatology syndrome. It was found that some of the information has not so far been available in literature. The use of these plants to treat dermatology syndrome is still needed by the communities, because of poor socio-economic conditions the high cost and a difficult access to allopathic medicines. Based on the studies and field experiences it can be concluded the detailed scientific experiments are urgently needed to evaluate the efficacy of dermatology syndrome.

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CHANGES IN THE MANIFESTATIONS OF SKIN DISEASE IN PATIENTS WITH NERVE DAMAGE

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Neurogenic inflammation has been implicated in the pathogenesis of various common conditions that affect the skin. We have conducted a systematic review of Pubmed to identify reported cases of alterations in the manifestations or distribution of skin disorders in patients with acquired central or peripheral neural damage or dysfunction. In the majority of these cases, inflammatory skin lesions spared dermatomes innervated by damaged nerves. These cases highlight the importance of neural innervation and neurogenic inflammation in the development of common dermatologic diseases.

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FICIN, A PLANT PROTEASE, IS A POTENT PRURITOGEN

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Background: Cysteine proteases derived from plants are known to cause itch in humans. Previously, we demonstrated that proteases derived from fig, papaya and pineapple (ficin, papain and bromelain respectively) cleave the extracellular N-terminus and thereby activate protease-activated receptor (PAR) 2, a member of the PAR family implicated in itch signaling. Whether these compounds induce itch in mice, and if so, by what mechanisms are unknown. *Objectives*: 1) To determine the ability of ficin to induce itch in mice. 2) To determine the role of PAR2 signaling in ficin-induced itch. *Methods*: Purified ficin was injected in the cheek of wild type (WT) C57Bl6 and PAR2 knock out (PAR2KO) mice. Scratching behavior was recorded and analyzed. *Results*: Ficin elicited robust scratching in both WT and PAR2KO mice compared to baseline and control injections with saline. WT mice exhibited higher scratching bouts than PAR2KO mice, however the difference between groups was not statistically significant. Ficin also caused edema surrounding the injection site within minutes of delivery in WT mice, a reaction not observed in response to other plant proteases or control injections. Ficin-induced edema was not observed in PAR2KO mice. *Conclusions*: Ficin is a potent pruritogen in mice. PAR2 activation contributes to protease-induced swelling but is not the major mechanism underlying ficin-induced itch.

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STUDIES ON CHEMICAL CHARACTERISTICS AND BIOACTIVITIES OF PLANTS COLLECTED FROM CENTRAL PARK IN MANHATTAN, NEW YORK

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Prescience Trust Funds, Phoenixville, Pennsylvania, USA

United States of America is one of the seventeen mega-diverse countries of the world having rich vegetation with a wide varies; scientific studies of plants have been initiated because of their contribution to healthcare. Extensive chromatographic separation and purification of extracts from the plants of Central Park in Manhattan New York have yielded a wide variety of structurally unique and biologically active secondary metabolites. Over the years it has been possible to isolate secondary metabolites like terpenes, steroids, flavonoids, megastigmanes, benzohydrofurans, phenylethanoids and their glycosides: saponins, free amino acids plus small molecular peptides, and soluble dietary fibres from the plant extracts. The structure elucidations of the isolated constituents were characterized by ultraviolet (UV), nuclear magnetic resonance (NMR), and multiple sclerosis (MS) experiments. The studies showed that plant extracts are complex in nature which contains diversified molecules. Chemical constituents present in the active extracts were also found to be different in chemical nature. Biological testing showed wide variation in activities. In addition bioassay studies have shown potential medicinal values of the plant extracts. Overall the studies have been a strong evidence for the United States of America as a promising source of natural products.

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ASSOCIATION OF HAPLOTYPES DEFINED BY THREE POLYMORPHISMS OF THE IL-31 GENE: -2057, -1066 AND IVS2+12, WITH PRURITUS AND SEVERITY OF ATOPIC DERMATITIS IN THE POLISH POPULATION

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IL-31 is one of the cytokines involved in the induction and maintenance of pruritus in atopic dermatitis (AD). We investigated the association of IL-31 haplotypes with pruritus and severity of AD, as well as their correlation with the serum IL-31 levels. 127 patients with AD and 96 controls were analyzed for IL-31 variants (-2057, -1066 and IVS2+12) using amplification refractory mutation system (ARMS-PCR). IL-31 haplotype frequencies were estimated with the use of tagging SNPs, EM and ELB algorithms. Serum IL-31 levels were measured using standard ELISA kit. The frequency of AAG, AGA, AGG, GAA haplotypes was significantly higher in patients with AD than in the controls. The mean IL-31 serum levels were lower in controls than in the patients ($p<0.00001$) and were significantly higher in those with severe vs. mild AD ($p=0.008$). No correlation was found between IL-31 serum levels and severity of pruritus. The haplotype AAA was associated with high IL-31 serum level ($p=0.008$) and with severe SCORAD ($p=0.013$). Haplotype GAA ($p=0.016$) was associated with severe form of pruritus, and the haplotype GGG ($p=0.07$) with a mild one. Our data suggests that the severity of AD in the Polish population is associated with specific haplotypes of the IL-31 gene.

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EVALUATION OF ITCH-INDUCING MEDIATORS IN CTCL

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Chronic pruritus is a common symptom affecting many individuals with lymphoma, particularly those with cutaneous T-cell lymphoma and Sezary syndrome. Effective control of pruritus in those patients is often difficult to achieve as antihistamines may show little benefit. Newer therapies, including aprepitant, have been proposed as effective measures, working outside of the classical histamine pathway. However, full characterization of non-histaminergic pathways in the peripheral nervous system has not been completed. Nociceptors in the skin representing subsets of dorsal root ganglion-derived have been identified as a relevant pathway carrying messages of itch and pain to the brain. Measurement of neuronal activity can be assessed *in vitro* using primary dorsal root ganglion (DRG) neurons from mice. Stimulation of particular subsets of ion channels (TRP, transient receptor potential channels) within these neurons causes action potential generation and neuronal activation. Here we evaluate the distribution and functional activity of candidate TRP-family ion channels in mouse skin and DRG neurons. Additionally, the effects of non-histaminergic pathways leading to nociceptor activation were investigated, including relevant itch-associated cytokines.

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ITCH CHARACTERISTICS IN PATIENTS WITH SCABIES

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Scabies is a frequent skin disease. Although it is the commonest symptom, the clinical aspects of pruritus have not been explored in this disease. The aim of this study was to characterize the clinical pattern of itch in adults subjects with scabies. A total of 19 patients (9 females, 10 males) with pruritus secondary to scabies, age range 18-60 years (mean age 29) were included in the study. Diagnosis was confirmed by dermatological examination, then each patient completed a questionnaire about clinical features of itch. 95% patients experienced itch every day. Itch was most frequent at evening (89%) and night (83%) compared to morning (61%) and afternoon (45%). Participants reported a mean itch intensity of 4 out of 10, and 8.3 in the worst moment. The most common symptoms accompanying itch were pain (58%), heat sensation (37%) and sweating (37%). The most frequent associated sensory symptoms were stinging (79%), tickling (68%) and burning (74%). Stress, dryness, sweat, hot water were the most common factors exacerbating pruritus Experience of scratching was reported as pleasurable in 47%, neutral in 6% and unpleasurable in 35%, for 12% of patients it was both pleasurable and unpleasurable. Scratching lesions were present in 63% of patients.

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PAR-2 OVEREXPRESSION IN KERATINOCYTES LEADS TO ENHANCED NEURO-EPIDERMAL INTERACTION AND PERIPHERAL SENSITIZATION WITH AN ATOPIC DERMATITIS-LIKE PHENOTYPE

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PAR-2 has been shown to play a pivotal role in various inflammatory skin diseases. However, the precise role of a keratinocyte-specific PAR-2 still awaits clarification. Therefore, we have generated mouse overexpressing PAR-2 in keratinocytes (KC-PAR-2OE) and examined its phenotype with respect to pruritus and neuro-epidermal communication *in vivo* and *ex vivo*. Those mice developed severe pruritus, dry skin and eczematous skin lesions with characteristic atopic-like dermatitis. This phenotype could be triggered also by house dust mite application, a typical allergen in atopic dermatitis. Moreover, besides a histologically highly inflamed and infiltrated skin, the keratinocyte-specific PAR-2 overexpression led to a peripheral neuronal sensitization indicative of enhanced sensory innervation as well as a phenomenon called hyperknesis. Altogether, our mice show similarities to

AD patients suggesting that proteases and keratinocyte-PAR-2 are critically involved in the pathophysiology of pruritus and atopic dermatitis. KC-PAR2 is an important link in neuro-epidermal communication with the keratinocyte protease-PAR2 system as a forefront of sensory signalling and neuro-immune communication in skin diseases such as atopic dermatitis.

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EVOKED ALLERGEN ITCH MODULATES BRAIN FUNCTIONAL CONNECTIVITY IN ATOPIC DERMATITIS PATIENTS

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Itch in atopic dermatitis (AD) is induced by allergens and involves central sensitization. The brain's "itch matrix" includes the putamen (also associated with the urge to scratch), the anterior cingulate and insular cortices (part of the emotional salience network), the dorsolateral prefrontal cortex, and other regions. However, how these different brain areas interact with one another is still unknown. We used resting-state functional connectivity brain imaging while varying itch level to investigate correlated activity across different regions of the "itch matrix". We performed 6-min BOLD fMRI scans in 14 AD patients before and after allergen prick induced itch. A seed-based analysis revealed reduced functional connectivity from the baseline resting state to the itch-induced state between putamen and anterior and mid-cingulate cortex, between anterior insula and posterior cingulate cortex, and between globus pallidus and mid-cingulate cortex, with decreased connectivity significantly correlated with increased levels of perceived itch. Evoked itch also increased connectivity between superior parietal lobule and dorsolateral prefrontal cortex, which correlated negatively with higher perceived itch. Itch appears to reduce connectivity between itch matrix regions and increase connectivity between executive attention processing regions. These results provide the first evidence of itch-related changes in brain functional connectivity in AD.

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THE CORTICAL CODES OF ITCH RELATED QUALITIES AS FOUND IN FMRI DATA

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During the last years some imaging studies on the cortical processing of itch have been performed and described more or less the same brain regions independently from the type or intensity of sensation evoked. Our hypothesis was that quality aspects of a sensation are coded by certain combinations of activity within the network of involved brain regions. Itch was induced using native cowhage spicules or inactivated spicules loaded with histamine or capsaicin and regularly interrupted by scratch bouts. Standard fMRI sequences were used to record cortical BOLD signals. After each sequence the subjects rated several stimulus qualities. The activation intensities of affected brain regions were put into a linear stepwise regression model to predict the ratings of the subjects. The scratch related activity of 4 brain regions only was sufficient to predict the intensity of itch induced by histamine (coefficient of determination $R^2>0.99$), capsaicin ($R^2>0.97$) and cowhage ($R^2>0.96$). Using itch related activity the regression model was less effective in predicting itch intensity (histamine: $R^2>0.66$, cowhage: $R^2>0.64$, capsaicin: no significant model found). Qualities of itch related sensations are coded in and can be predicted by a combination of the activation of the brain areas which are involved in the processing of the respective stimulus.

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SCRATCHING-INDUCED PLEASANTNESS: A HUMAN FMRI STUDY

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To scratch itchy skin is pleasurable. However, the underlying cerebral mechanism of this phenomenon is little understood. Thus, with sixteen healthy subjects, this issue was investigated using functional magnetic resonance imaging in this study. Pleasurable feeling was evoked when the wrists where electrical itch stimuli were applied was scratched, while not when the dorsal forearms, far from itch stimuli, were scratched. The reward system was significantly activated while pleasurable feeling was evoked, indicating that this system is associated with scratching-induced pleasantness. Moreover, we also observed significant activations of motor-related regions, even though unpleasantness of itch disappeared after scratching. Probably, this activation could reflect the desire to scratching to get further pleasantness.

128 Duplicate.

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THE EFFECT OF EXCIMER LIGHT ON HYPERESTHESIA IN ATOPIC DERMATITIS

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Itch is a major problem in management of atopic dermatitis (AD), and reduction of the itch sensation threshold (alloknesis) in AD patients makes the symptom intractable. Although excessive response to warmth or light mechanical stimuli has been thought of as alloknesis, there is no established method to improve such conditions. The aim of this study is to investigate the effect of targeted 308 nm UVB irradiation by excimer light on hyperesthesia in AD. Thirteen patients with atopic dermatitis who showed resistance to topical steroid and oral antihistamines were enrolled to this study. Irradiation with excimer light was performed once a week for 2 months. Treatment effects are evaluated by local eczema area and severity index (EASI) score, threshold of hyperalgesia measured with instrument for algesimetry, visual analogue scale (VAS), and thermal hyperalgesia before treatment and 2 months after the initiation of treatment. Except for one case, EASI score improved in all cases. Itch intensity evaluated with VAS scoring improved in all cases except three cases. To our surprise, threshold for hyperalgesia was significantly improved after irradiation. Thermal hyperalgesia against warmth was observed in many cases, and was improved in ten cases.

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ITCH RELATED TO CHRONIC WOUNDS: WHAT INTERVENTIONS ARE USED, WHAT INTERVENTIONS AGGRAVATE WOUND-RELATED ITCH

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Introduction: Itch related to chronic wounds is familiar to persons with chronic wounds and their clinicians, but is not well described in the literature. *Purpose:* The purpose of this study was to explore the problem of itch as it occurs with chronic wounds, particularly to ask persons with chronic wounds what interventions are used and what aggravates wound-related itch. *Methods:* Participants (*n*=199: 112 men, 170 Caucasians, mean age 67 years) with wounds being followed at an outpatient wound treatment center were interviewed one time, face-to-face, by the primary investigator using the Paul-Pieper Itching Questionnaire. *Data Analysis:* Descriptive statistics were used. *Results:* Of the 199 participants, 59 responded regarding interventions used for wound-related itch. Scratching (24%) and rubbing (14.5%) were used most often in response to wound-related itch, followed by calamine (10%), petroleum gel (4.5%), and distraction (4.5%). Heat (2.5%) and dressing removal (2.5%) were found to exacerbate wound itch. *Conclusion:* Wound-related itch can be bothersome enough that interventions are taken to relieve it. Rubbing and scratching may be deleterious to the wound and surrounding skin. Health care providers should assess persons with chronic wounds for itch and offer interventions to provide relief and promote wound healing.

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REDUCTION OF LOCAL PROINFLAMMATORY ITCH MEDIATORS

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A prospective, double-blinded, pilot study in 23 burn survivors randomized to control moisturizer or moisturizer containing protease enzymes demonstrated statistically significant differences for itch duration, weekly frequency, itch episodes per day, itch TBSA and reported affective burden of itch after treatment. Increased tissue inflammation may perpetuate post-burn pruritus. The test moisturizer proteases can degrade excessive amounts of proinflammatory factors. The purpose of this *in vitro* study was to further explore the ability of specific proteases to deactivate or activate known proteins associated with inflammation or healing. Purified human target proteins were incubated in a control or two test solutions and samples removed at various time points up to 24 hours. Blinded samples were tested using a novel infrared protein multiplex sandwich-ELISA-type array technique. The two test solutions gave similar near 0 pg/ml immediate reductions in TNFα, IL10 and IL23 concentrations. Both test solutions reduced the concentrations of MMP1, MMP9, MIP1a, IL6 and IL6R compared to control. Both FGFb and GDNF test solution concentrations remained more elevated than control. Prior *in vitro* work showed Substance P concentration is reduced when incubated with test proteases similar to TNFα. These results suggest that specific proteases may disrupt inflammatory factors that contribute to pruritus.

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CAPSAICIN CAN ACTIVATE NEURONS IN A RE-INNERVATED SKIN EXPLANT MODEL AFTER IT IS DEPOSITED ON THE EPIDERMIS

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Using an *ex vivo* skin-nerve preparation, skin and nerve cells were reconstituted into a single unit and maintained in a nutrient media bath until required experimentally. This experimental model system is not possible with human subjects. Our objective was to use the epidermis as a relay for the induction of an electric current to the neurones following the topical application on the epidermis of the skin of capsaicin, an agonist of the TRPV1 channel implicated in pruritus and pain. After 10-20 days of co-culture to form the re-innervated skin model, we applied a solution of capsaicin directly in the epidermis of the skin (4 µM). The resulting current was recorded using a path-clamp technique on the neuronal fibres. Following the topical application of capsaicin, spontaneous activity was triggered, as characterised by repetitive spikes with a period of 125, 225 and 275 ms. This study demonstrates that the skin explant and nerve cells preparation may recept stimuli.

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ADHERENCE TO TREATMENT IN CHRONIC ITCH PATIENTS

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Adherence to treatment is of increasing importance in daily clinical-practice, especially in regard of treatment-efficiency. Adherence is defined as the degree to which patients use medication as described by their healthcare-provider, giving the patient an active role in achieving therapeutic aims. Non-adherence not only causes increased costs but also, and more importantly, negatively affects patients' health: it may cause long-lasting, inefficient treatment which leads to patient-frustration and dissatisfaction. After long being ignored, adherence is becoming an acknowledged problem throughout the different fields of medicine, including dermatology. Nonetheless, adherence to treatment is still an underestimated topic in patients suffering from chronic-itch. There are several reasons for non-adherent behaviour in itch-patients which still need further exploration. As data of 26 chronic-itch patients at the itch-clinic Heidelberg suggests, subjective illness perception plays an important role regarding adherence in chronic-itch patients. Patients often feel misunderstood or not taken seriously by health-professionals. Results from our qualitative-interviews lead to the conclusion that chronic-itch is an empathy-sensitive-symptom with psychosocial effects. Focusing on the patient's subjective burden and degree of impairment in order to better understand fears and problems may prevent non-adherence. Further research is needed on how to increase adherence to treatment in patients suffering from chronic-itch.

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PHYSIOLOGICAL AND BEHAVIORAL RESPONSES TO PRURITOGENS IN THE ABSENCE OF PROTEIN KINASE-Cδ

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Itch is an unpleasant sensation that elicits the urge to scratch and can present as a debilitating symptom of various dermatological, neurological, and systemic diseases. Itch-producing compounds known as pruritogens stimulate receptors located on C-fibers that innervate the skin and mucous membranes. Most currently known pruritogen receptors are Gq-Protein Coupled Receptors (GqPCR), which activate the canonical Phospholipase C (PLC) pathway, generating IP3 and Diacylglycerol (DAG). The specific isoform PLCβ3 is coupled to the histamine H1-receptor, but little is known about the intracellular signaling molecules further downstream and at other pruriceptors. Here, we investigated the role of Protein Kinase-Cδ (PKCδ) as an intracellular mediator of itch signaling in response to various pruritogens. We previously examined PKCδ-knock out (KO) mice in acute tests of mechanical and heat nociception and found no significant change from wild type controls. Immunohistochemistry (IHC) was used to characterize the distribution of PKCδ in mouse dorsal root ganglion (DRG) cells. PKCδ expression was restricted to small diameter cells and half of PKCδ-positive cells co-stained for IB4, while a smaller number expressed CGRP. We are currently using *in vivo* and *in vitro* techniques to characterize the effects of genetic deletion and pharmacological inhibition of PKCδ on itch.

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EFFECTS OF PRURITIGENS ON ACUTE ITCH IN TRPV1/TRPA1/TRPM8 KNOCKOUT MICE.

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TRP channels are known to be important regulators of itch and pain. The role of TRPV1 in histamine-induced itch was shown with a TRPV1 knockout mouse. Here we use a triple knockout model (TRPA1/TRPV1/TRPM8 -/-) to investigate the itch transmission pathway and TRP channels in more detail. We used the LaMotte check model to investigate the pruritic effects of histamine, serotonin, endothelin-1 and chloroquine in triple TRP KO mice. Itch responses were reduced in triple TRP KO mice to histamine, serotonin and endothelin-1. No differences with respect to prestimulation scratching controls were found. Interestingly, electrophysiology studies using DRG cells from triple TRP KO mice showed increased histamine-induced cell signaling for Ca2+. Our results also show a gender-specific finding of chloroquine-induced scratching behavior with significantly higher scratching bouts for triple TRP KO males over females. The triple knockout mouse model is a very valuable tool to identify and decode pruritic pathways, including the chloroquine-induced itch pathway.

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BARBITURATES INDUCE SCRATCHING BEHAVIOR IN MICE WITH ATOPIC DERMATITIS: AN ANIMAL MODEL FOR MIMICKING NOCTURNAL SCRATCHING IN ATOPIC DERMATITIS?

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We have previously shown that hairless mice fed a special diet, HR-AD, develop atopic dermatitis-like symptoms, and that orally administered ethanol markedly enhances scratching behavior in HR-AD-fed mice possibly via central nervous system depression. The aim of the present study was to examine whether barbiturates, which have similar actions to ethanol, induce scratching behavior in several itch models, and to elucidate the mechanism of action. Intraperitoneal administration of barbiturates, such as pentobarbital and phenobarbital, significantly and dose-dependently induced scratching behavior in HR-AD-fed mice but not in normal mice. Furthermore, barbiturate administration increased scratching behavior in NC/Nga mice, an atopic dermatitis model, but not histamine-induced scratching in normal mice, suggesting that barbiturate-induced scratching may be associated with chronic itch disease. Barbiturate-induced scratching was inhibited by either γ-aminobutyric acid type A receptor (GABAAR) antagonist or L-type voltage-dependent calcium channel (L-VDCC) agonist. However, positive modulators of GABAAR, benzodiazepines alone only slightly increased scratching. Additionally, a selective GABAAR agonist, muscimol alone did not at all. Therefore, synergistic action of GABAAR activation and L-VDCC inhibition could mediate the barbiturate-induced scratching. Since barbiturate is one of hypnotics, barbiturate-induced scratching in mice with atopic dermatitis may mimic nocturnal scratching in atopic dermatitis patients.

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BANGLADESHI-AMERICAN PARTICIPATION IN TELOMERE LENGTH STUDIES: A META-ANALYSIS FROM NEW YORK

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Telomere length in individuals is highly variable, and studies have shown that shortened telomeres are associated with poor prognoses in many diseases, including cancers and other diseases that disproportionately affect Bangladeshi-American. There is also strong evidence that environmental and behavioral factors can play an epigenetic role in telomere length homeostasis. Chronic stress is associated with shorter telomeres in women, but studies have not been explicitly done to assess the role of chronic stress in men. We hypothesize that telomere length can be used as a diagnostic indicator of health status, and the average telomere length are shorter in Bangladeshi-American men due in part to higher levels of chronic stress. To test this hypothesis, we examined the telomere length of DNA from peripheral blood mononuclear leukocytes of more than 39 Bangladeshi-American men and administered a stress studies to assess chronic stress levels. Preliminary analysis of the data

indicates a potential negative association between stress and telomere length, though the studies are not significant. We also observed a significant negative correlation between telomere length and BMI. The studies indicate that environmental factors can affect telomere length in Bangladeshi-American men, and that telomere length may be a useful health status indicator in Bangladeshi-American.

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PARTICIPATION AMONG THE BIHARI REFUGEE CAMP PATIENTS WITH SKIN DISORDERS: INVESTIGATIONS FROM THE MIRPUR AREA OF DHAKA BANGLADESH

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Because of living conditions in Bihari refugee camp of Bangladesh, skin disorders like dermatosis, acne, eczema, keratonosis, prurigo, and vitiligo are common. Traditional medicinal practitioners (TMPs) provide primary healthcare to most of Bihari population in Bangladesh and they use medicinal plants for this purpose. The investigations were carried out in Bihari refugee camp, Mirpur, Dhaka, Bangladesh to collect information on medicinal plants used to treat skin disorders like dermatosis, acne, eczema, keratonosis, prurigo, and vitiligo. Medicinal plant samples as pointed out by the TMPs were collected and identified at the Bangladesh National Herbarium. These medicinal plants included Aconitum napellus L., Agaricus campestris L., Azadirachta indica A.Juss., Cyrtandra cupulata Ridl., Curcuma longa L., Glycyrrhiza glabra L., Lasia spinosa (L.) Thwaites, Linum usitatissimum L., Lens culinaris Medik., Nigella sativa L., Ocimum tenuiflorum L., Olea europaea L., Panax ginseng C.A.Mey., Plantago major L., Pongamia pinnata (L.) Pierre, Scoparia dulcis L., Tagetes patula L., and Uvaria rufa Blume. It was noted in the investigations that the patients were quite satisfied with treatment by the TMPs. The investigations suggest that modern scientific inquiries have the potential of discovering new antimicrobial compounds in the above-mentioned medicinal plants, which can be effective against microorganisms causing skin illnesses.

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INVESTIGATING THE PREVALENCE OF ITCH IN HAEMODIALYSIS PATIENTS

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Itch is a frequent symptom in patients on haemodialysis. Decades ago, up to 85% of haemodialysis-patients suffered from uraemic itch, but improved haemodialysis technology and effectiveness has decreased the prevalence. However, worldwide variations from 20 to 70% are known. Representative epidemiological studies do not exist. In order to investigate the prevalence of itch in haemodialysis-patients, we developed a study-design to answer this question sufficiently. First of all needs of haemodialysis-patients suffering from itch were identified by conducting qualitative interviews in a pre-study. Information relying on these interviews as well as expert-opinions, experimental, laboratory, epidemiological and own expertise gained from previous itch-studies served to develop patient-oriented questionnaires aiming to measure the prevalence of itch. Thereby several validated instruments for use in large-scale studies (e.g. questionnaire for chronic itch in general population and SF-12) were considered. In a second step reliability of developed questionnaires was proofed within 20 haemodialysis-patients. To ensure a representative study-design special statistical methods are necessary considering random cluster-sampling according to geographical distribution of haemodialysis-units in Germany. Calculation of power and sample-size are also necessary. Investigating the prevalence of itch in haemodialysis-patients demands information on co-diseases, general well-being, QoL and dermatological characteristics. We present a representative epidemiological study-design based on cross-sectional analysis.

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EPIDEMIOLOGY OF ITCH

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Epidemiological data on acute and chronic itch are sparse. However, itch is the most frequent symptom in dermatology and other fields of medicine. Nevertheless, there are few true epidemiological studies on itch. Especially during the last years, epidemiological data on chronic itch in the general population has increased. Published studies show that the symptom of itch is highly prevalent. Just recently, new important data were published including, for the first time, an estimate of the 12-months cumulative incidence of chronic itch as well as its determinants. In this paper, we summarize recent advances in epidemiology of itch, considering the general population as well as specific diseases.

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THE BIBLIOMETRICS OF ITCH: 2013 UPDATE

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In 1965, only 13 articles about itch/pruritus were published; this number increased to 111 in 2012. Pruritus is used more frequently than itch in article titles. During 2011–2012, Acta Dermato-Venereologica published the largest number of itch articles, followed by Seminars in Cutaneous Medicine and Surgery, BJD, Hautarzt, and PLOS ONE. For articles published during 2011–2012, Dong accumulated the largest number of itch article citations, 85. Wilson and colleagues published the most cited itch article during the same 2 year period (Nature Neuroscience, 2011, 14, 595–602). Documents on itch appeared 3 times in NEJM, 3 times in Pain, 2 times in PNAS, once in JCI, once in Science, and not at all in Lancet or Nature during 2011 – 2012. Hägermark and colleagues published the most cited itch article since 1965 (JID, 1978, 71, 233–235). Schmelz, with 1277 total citations, is the most cited author of itch articles published since 1965. Second and third in this category are Bergasa and Jones. The h-index measures the cumulative impact of an author's publications, assessing both the total number of articles (productivity) and number of citations per article (quality). The authors with the highest itch article h-indices since 1965 are Yosipovitch, Kuraishi, and Hägermark.

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PAIN MANAGEMENT KNOWLEDGE AMONG DERMATOLOGISTS

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Introduction: Pain is a prevalent syndrome in most of the pathological conditions and diseases. Effective pain management largely depends on adequate knowledge of medical doctors of all specialties, including dermatologists. Itching very often is accompanies with depression and pain while skin specialists rather pay attention to itching than to pain. It presented an interest to determine pain management knowledge level among dermatologist. *Methods*: Descriptive epidemiological study was conducted. Special questionnaire with open and closed questions was developed and disseminated among skin specialists. Dermatologists were selected non-randomly in 14 regions of the country. *Results*: 91% of the study participants have not employed WHO Pain Relief Ladder in practice. Most of them were unaware about the pain assessment scales. In the vast majority of the cases patients were not prescribed pain killers but only itching relief medicine. None of them have been trained in pain assessment and management. There was a serious lack in national guidelines for pain management in dermatology. *Conclusion*: Study results stressed the need to elaborate national pain management regulatory documents in dermatology and introduce training courses for skin specialists.

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ASSESSMENT OF EFFICACY OF THERAPIES FOR THE PRURITUS OF CHOLESTASIS: EVALUATION OF THE VISUAL ANALOGUE SCORE

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Background: A visual analogue score (VAS), based on application of a visual analogue scale, has been widely used to assess pruritus in clinical studies of patients with cholestatic liver disease. A VAS is a numerical score of the severity of the perception of pruritus, and, hence, is inherently subjective. *Objective*: To assess the reliability of a VAS as an index of pruritus in cholestatic patients. *Methods*: In 8 patients with chronic pruritus due to primary biliary cirrhosis values for a VAS of pruritus were compared with corresponding measurements of scratching activity, which were generated by a monitoring system specifically designed to quantitate this activity. *Results:* The mean Spearman Rank correlation coefficient between individual values for the VAS and corresponding mean values for scratching activity was 0.072; the range of these coefficients was 0.04 to 0.26. *Conclusions*: A VAS of pruritus is an unreliable index of scratching activity, and, hence, of the pathophysiological process responsible for the pruritus of cholestasis. Use of a VAS as a primary quantitative endpoint in trials of the efficacy of potential therapies for the pruritus of cholestasis may be inappropriate.

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SELECTIVE PHOSPHATIDYLINOSITOL 3-KINASE γ (PI3Kγ) INHIBITOR REDUCES ACUTE AND CHRONIC SCRATCHING BEHAVIOR RELATED TO THE ACTIVATION OF GASTRIN-RELEASING PEPTIDE RECEPTOR (GRP-R) IN MICE

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We investigated the involvement of PI3Kγ pathway in acute or chronic scratching behavior mediated by GRP-R (BB2 receptor) activation in mice. Acute scratching behavior was elicited by intrathecal injection of GRP or bombesin (1 nmol/site), or intradermal injection of GRP (1 nmol/site) into the back of the neck. As a model of chronic pruritus, we used the dry skin itching paradigm. The animals were orally treated with the selective PI3Kg inhibitor AS605240 (0.1–10 mg/kg) or saline solution (negative control). AS605240 produced a marked and significant reduction of scratching behavior elicited by intrathecal injection of GRP. The inhibition percentages were between 75 and 90%, depending on the dose tested. In addition, AS605240-treated animals (3 mg/kg) visibly decreased the scratching behavior induced by bombesin (agonist of BB1 and BB2 receptors). Interestingly, AS605240 also promoted a marked reduction of scratches after intradermal application of GRP (54±5%). Finally, AS60524 significantly reduced the scratches observed in the dry skin model, with inhibition percentages between 60 and 62%. Our data suggests that AS605240 treatment is effective in preventing acute and chronic pruritus in mice. Other studies are being conducted to further investigate the role of PI3γ in GRP-R-mediated itching mechanisms.

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EVALUATION OF THE EFFECTS OF A PURIFIED MARINE EXOPOLYSACCHARIDE ON GENE EXPRESSION IN A MODEL OF PSORIATIC EPIDERMIS

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Psoriasis is an inflammatory skin disease characterized by an abnormal keratinocyte proliferation and differentiation. It may be induced and maintained by cytokines produced by activated resident and recruited inflammatory cells in lesional psoriatic skin. We developed and evaluated an original purified marine exopolysaccharide (MEPS), composed mainly of galactose and N-acetyl glucosamine, and secreted by a marine plankton microorganism. Its effect on gene expression was evaluated using an original 3-D model: a Human Reconstituted Epidermis (RHE) stimulated by a mix of cytokines (IL-17, TNFα, OSM), in order to mimic psoriatic epidermis. The RHE was treated or not by the MEPS at 0.01%, and incubated for 48 h before measuring gene expression by a specific RT-qPCR array. We demonstrated that

the MEPS improves the epidermal reconstitution, by stimulation of the proteins of the epidermal differentiation complex (EDC), proteins of adhesion and the antimicrobial peptides. It also decreases the expression of genes involved in inflammation which are stimulated in psoriatic epidermis. Applied at the surface of a psoriatic epidermis, it counteracts the skin disorders linked to inflammation, differentiation and proliferation disorders. According to these results, the MEPS could be considered as a promising ingredient for dermo cosmetic products for acting on skin restructuration.

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GENDER DIFFERENCES IN CHRONIC PRURITUS: RESULTS OF AN INITIAL RETROSPECTIVE STUDY

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Gender differences have been widely neglected in chronic pruritus (CP). The aim of our study was to compare multiple clinical parameters of CP in a large representative collective of patients and to assess any gender differences. Data of 1,037 patients (54.8% women) were extracted from our multi-dimensional database. Men were significantly older (p<0.001) than women though no difference was found in the overall duration of CP. Concerning the underlying diseases leading to CP, men had more often dermatologic and systemic diseases while women had more neuropathic and psychosomatic diseases underlying CP. Women significantly more often showed a worsening of the CP by emotional (p=0.002) and psychosomatic factors (p=0.046). Women obtained higher visual analogue scale scores (p=0.031), reported more painful qualities (p<0.05), a higher impact on quality of life (p=0.033), and had significantly more often prurigo nodularis (p=0.001) than men. Gender-specific differences were found in the quality, localisation, and triggering of CP but also in the underlying disease and scratching behaviour. These facts must be taken into account in the medical care of CP patients and when conducting any kind of clinical research on itch.

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COMPETENCE CENTER CHRONIC PRURITUS AT THE UNIVERSITY HOSPITAL OF MÜNSTER: A DEDICATED CENTER WITH A DECADE OF EXPERIENCE IN MULTIDISCIPLINARY MEDICAL CARE

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Because of the complex nature, and difficult-to-establish etiology of chronic pruritus (CP), medical care of CP patients is challenging. It is obvious that this challenge can only be met with a multidisciplinary approach. Taking account of this fact, the first Itch Clinic in Germany was established at the University Hospital of Münster in 2002 to provide the best possible multidisciplinary medical care. Currently, over 2,200 outpatients and over 350 inpatients are diagnosed and receive treatment at this center each year. To ensure easy and rapid evidence-based medical care, an electronic system for medical documentation and patient questionnaires was established. Data transfer from the electronic health records into a database allows clinical research including large item and correlation analyses. Our combined multidisciplinary expertise in treatment of CP patients substantially contributed to establish the current CP guidelines. Translational research has resulted in identification of novel target-specific therapies (e.g., neurokinin 1-antagonist). The center also carries out basic research with the goal of characterizing peripheral and central itch mechanisms. Thus, the multidisciplinary approach, combined with basic, clinical and translational research enables comprehensive medical care of patients as well as planning and implementation of controlled clinical trials.

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SCROTAL LICHEN SIMPLEX CHRONICUS: TREATMENT WITH 0.1% TACROLIMUS OINTMENT

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Objective: To evaluate the efficacy of topical 0.1% tacrolimus ointment in the treatment of scrotal lichen simplex chronicus. *Methods*: A prospective, open-label study in which adult patients applied 0.1% tacrolimus ointment twice daily for 6 weeks. Before treatment and at 6 weeks, subjects were assessed subjectively on the severity and frequency of itch, degree of itch-induced sleep impairment and disease-related quality of life, and objectively on the clinical disease severity by a single investigator. *Results* (interim): 35 subjects, with a mean age of 48 years, participated. 75% attended the second visit at 6 weeks. There were improvements in mean itch score (maximum 10) from 6.7–2.9, mean itch frequency from 14.8–3.4 times per week, mean sleep score (maximum 5) from 2.8–1.1, mean Dermatology Life Quality Index score (maximum 30) from 9.6–3.5, mean disease severity score (maximum 6) from 3.5–1.4, and reduction in mean scrotal surface area involvement from 80–50% post-treatment. All improvements were statistically significant (p<0.05). The mean onset of action was 4.6 days. No major adverse effects were reported except for 5 (14.3%) who experienced intolerable burning sensation. *Conclusion*: Topical 0.1% tacrolimus ointment, when tolerated, was an effective and safe treatment for scrotal lichen simplex chronicus in our study population.

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NALBUPHINE ATTENUATES ITCH IN THE SUBSTANCE P-INDUCED MOUSE MODEL

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Nalbuphine is a mixed mu antagonist/kappa agonist opioid. The effect of Nalbuphine on substance-P (SubP) induced scratching was studied in the mouse model. This model is relevant to antihistamine-resistant pruritus and is observed in patients with various dermatopathologies. Studies were conducted in male C57BL/6 mice treated subcutaneously (SC) dosed with vehicle (phosphate buffered saline, PBS) only or nalbuphine (10–30 mg/kg). Mice received either PBS or SubP (250 nM in 0.050 ml) injected intradermally into the rostral part of the back and video recorded. Itching was scored by counting the number of scratches over 30 minutes following SubP (or vehicle) challenge. Following SubP administration in the untreated mice, itching began within 3–5 minutes from the pruritogen administration with the highest itch intensity in the first 30 minutes post-Sub P. Following nalbuphine administration, a significant reduction in itch ($p<0.001$) was noted with a 43% reduction in itch at 10 mg/kg dose and 52% at the 30 mg/kg dose. Ambulation was not suppressed in mice injected with nalbuphine doses up to 30 mg/kg indicating that attenuation of scratching was not due to decreased locomotor activity. These data suggest that nalbuphine holds promise as a potential antipruritic in human conditions involving itch.

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CUTANEOUS EXPRESSION OF THE KAPPA OPIOID RECEPTOR IN PRURITIC DERMATOSES

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Translational research in chronic pruritus aims to identify potential candidates for a target-specific therapy in pruritic dermatoses which is urgently needed. A potential target candidate is the peripherally expressed kappa opioid receptor (KOR). The aim of the present study was to determine the cutaneous expression level of KOR in lesional, pruritic skin by means of immunofluorescence and western blot. In total, > 330 biopsies of different dermatoses (e.g., atopic dermatitis (AD), psoriasis (PSO), prurigo nodularis (PN), lichen planus, urticaria, mastocytosis, cutaneous T-cell lymphoma (CTCL)) have been analyzed and compared to healthy controls (HC). KOR was found in all patients mainly in the epidermal basal keratinocytes, and, suprabasally in AD, PSO, PN and lichen planus whereas dermal inflammatory cells expressed KOR only weakly. The signal in western blot analysis was significantly higher in AD ($p<0.05$) and CTCL ($p<0.05$) compared to HC. The levels in PSO were slightly down-regulated, with no difference seen between other dermatoses and HC skin. Further analysis with separated epidermis and dermis showed a main signal in the epidermis. Our results indicate that peripheral KOR is an interesting target especially in AD and CTCL. Current studies investigate the role of epidermal KOR using novel peripheral agonists.

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MECHANISMS OF ITCH: PROTEASES ACTIVATE MAS-RELATED G-PROTEIN COUPLED RECEPTORS

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Mas-related G protein coupled receptors (Mrgs) are expressed by small-diameter sensory neurons in DRGs and have been shown to contribute to the generation of itch. We describe cleavage and activation of Mrgs by cathepsin S. Cat S, an endogenous cysteine protease, has been shown previously to activate PAR2 and to induce itch in humans. Following treatment with cat S, HeLa cells transfected with MRGC11 demonstrate calcium transients and an increase in phosphorylated PKC expression. To determine that receptor cleavage occurred, we attached a luciferase tag at the N-terminus, transfected these into HeLa cells, and added Cat S. Cat S released the luciferase as detected by luminescence and western blot. Neither activation nor cleavage occurred when certain N-terminal receptor leucine residues were mutated to isoleucine. This finding suggests that these residues are critical for activity. A series of potential tethered peptides were generated based on the predicted cat S cleavage sites of the MrgC11 N-terminus. These peptides failed to induce signaling in cells expressing wild type MrgC11. These results indicate that Mrgprs can be activated by Cat S and suggest an additional cascade by which cat S signaling contributes to itch and cutaneous inflammation.

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ANALYSIS OF EXPRESSION OF DIFFERENT RECEPTORS POSSIBLY INVOLVED IN PRURITUS IN CANINE DORSAL ROOT GANGLIA

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As in humans, many skin diseases in dogs are accompanied by pruritus, a symptom often unsatisfactory controlled. Little is known about mediators and receptors that are involved in itch induction in dogs, and many substances that are well known to cause pruritus in humans and/or rodents do to not induce itch in dogs under experimental conditions. Species differences in itch induction might be explained by differences in receptor expression in the sensory nerves. The aim of the study was to analyze the expression of receptors for various pruritogenic mediators in canine dorsal root ganglia (DRG) on mRNA level. Expression of transient receptor potential vanilloid 1, tachykinin receptor 1, toll like receptor 7, endothelin receptor type A, opioid receptor μ1 and opioid receptor κ1, histamine H1–H4 receptors, neurotrophic tyrosine kinase receptors 1 and 2, proteinase activated receptor 2 as well as the IL-31 receptor complex was found in canine DRG with varying expression intensity. Interestingly, a strong signal of the IL-31 receptor complex was found in every dog analysed ($n=11$). Functional studies might clarify, why several ligands for the receptors found to be expressed in DRG do not induce scratching behaviour in dogs.

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TOPICAL APPLICATION OF QX-314 INHIBITS PRURITUS IN A MOUSE MODEL OF XEROTIC ECZEMA

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Primary afferent neurons expressing MrgprA3 are essential detectors of itch in many non-histaminergic pruritus conditions inclu-

ding atopic dermatitis, xerotic eczema (dry skin itch) and allergic itch. Clinical management of these conditions is challenging, as existing non-steroidal antipruritic therapies are often ineffective for MrgprA3-related pruritus. Recently we demonstrated a novel strategy to reversibly silence itch-detecting neurons by targeted delivery of the membrane-impermeant sodium channel blocker, QX-314, through pruritogen-activated large-pore ion channels expressed at the peripheral terminals of pruriceptors. We found that blocking histamine or non-histamine itch-sensing neurons with QX-314 did not alter pain thresholds or tactile sensitivity, demonstrating a selective silencing only of itch sensation (Roberson, et al., Nature Neuroscience, 2013). We now show that topical application of QX-314 inhibits scratching in a mouse model of xerotic eczema. These findings suggest that topical administration of charged sodium channel blockers may be an effective treatment for non-histaminergic pruritus.

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INVOLVEMENT OF KERATINOCYTE-PRODUCED HISTAMINE IN ACUTE AND CHRONIC ITCH-RELATED BEHAVIORS INDUCED BY TOPICAL APPLICATION OF ANIONIC SURFACTANTS IN MICE

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Itch is the most common side effect of cosmetics and toiletries and anionic surfactants may be their important causal constituents. We investigated whether topical application of anionic surfactants would cause itching in mice. Topical application of 1% and 10% sodium laurate increased hind-paw scratching (delayed scratching) between 2 and 3 h after application. Topical application of 10% sodium dodecyl sulfate (SDS) did not increase scratching between 2 and 3 h after application. However, it increased scratching about 24 h after application and its repeated application time-dependently increased scratching (chronic scratching). On the other hand, 10% N-lauroylsarcosine sodium caused neither delayed nor chronic scratching. Sodium laurate-induced delayed scratching and SDS-induced chronic scratching were inhibited by the H1 histamine receptor antagonist terfenadine (30 mg/kg, p.o.) but was not affected by mast cell deficiency. Histamine content and 53-kDa L-histidine decarboxylase level of the epidermis were increased 2 h after sodium laurate application and 4 days after the start of repeated SDS application. Repeated SDS application also increased the mRNA level of L-histidine decarboxylase in the epidermis. These results suggest some anionic surfactants induce acute (delayed) or chronic itching, which are mainly due to the increased production of histamine in the epidermal keratinocytes.

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TRANSCRIPTIONAL REGULATION OF THE HUMAN SEMAPHORIN 3A GENE IN NORMAL EPIDERMAL KERATINOCYTES: IMPLICATION OF APPLICATION TO INTRACTABLE ITCH IN ATOPIC DERMATITIS

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Increased epidermal nerve density is considered as one cause of intractable itch, suggesting that the lesional skin is susceptible to stimulation and sensitive to itching in the periphery. Previously, we reported a potential contribution of semaphorin 3A (Sema3A) to modulation of epidermal innervation in dry skin-based skin diseases such as atopic dermatitis. However, the regulatory mechanism of endogenous Sema3A is currently unknown. In this study, we investigated the promoter region of Sema3A gene in normal human epidermal keratinocytes (NHEK). The 5'-flanking region of Sema3A gene (approx. 1.4 kb) was cloned and identified a number of putative transcription factor binding sites by using a P-Match. Deletion analyses identified a critical region for Sema3A promoter activity within -134 bp from the transcription start site. However, -1444 /-974 regions showed significantly lower activity, suggesting the presence of a suppressor region. In addition, RORα, Jun, Fos, or Sox-4 siRNA effectively reduced Sema3A expression in NHEK, whereas NF-kB siRNA markedly increased Sema3A expression. These results indicate that RORα, AP-1 and Sox-4 binding to the promoter region are positive transcription factors, while NF-kB binding to -1444 /-974 regions is a suppressor. Our research may bring a new insight for identification of novel antipruritic drug target.

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PREVALENCE AND CHARACTERIZATION OF PRURITUS IN JAPANESE PATIENTS WITH HEMATOLOGICAL DISORDERS

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Pruritus is a common feature in some hematological disorders and usually accompanies diseases such as malignant lymphoma, polycythemia vera (PV), Sezary's syndrome, some forms of leukemia, multiple myeloma, mycosis fungoides and iron deficiency anemia. Pruritus is present in approximately 30% of patients with Hodgkin's disease and might precede the diagnosis by up to 5 years. Patients with Hodgkin's lymphoma complicated by pruritus have a poorer prognosis: their pruritus is invariably severe, sometimes with excruciating burning sensations, more frequently generalized. In PV, 30% to 50% of patients have pruritus. It is characterized by strong itching, stinging, tingling or burning sensations following contact with water (aquagenic) at any temperature without visible changes of the skin. Iron deficiency anemia can cause generalized pruritus, however, little is known about the exact frequency, characteristics and influence on quality of life of pruritus sufferers in Japan. Therefore, we investigated these aspects of Japanese patients with hematological disorders including malignant lymphoma, polycythemia vera and iron deficiency anemia using a patient-directed itch questionnaire. Our data are currently under analysis and will be expected to give the prevalence and characterization of pruritus in Japanese patients with hematological disorders.

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DYNORPHIN IS A NEUROMODULATOR REGULATING ITCH IN THE DORSAL HORN OF THE SPINAL CORD

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Scratching and other counter-stimuli provide immediate relief from itch. Moreover, brief counter-stimulation is associated with an anti-pruritic state that persists for minutes. However, the neuromodulatory mechanisms underlying the anti-pruritic state are completely unknown. Previously, we provided corollary evidence that a specific population of spinal interneurons (B5-I neurons) is required for normal itch sensation because Bhlhb5 mutant mice that lack B5-I neurons develop neuropathic itch. Here we characterize B5-I spinal interneurons, provide cause-and-effect evidence that B5-I neurons function directly to inhibit itch. Our data indicate that B5-I neurons express the SST2A receptor and that acute inhibition of B5-I neurons with a somatostatin analog results in elevated itch sensitivity and spontaneous scratching. In addition, a significant proportion of B5-I neurons express dynorphin, an endogenous kappa opioid receptor agonist, which we determine is crucial for mediating the inhibition of itch at the level of the spinal cord. Specifically, U50488 and nalfurafine, two kappa opioid agonists, inhibit scratching behavior in response to a variety of chemical pruritogens. Furthermore, kappa opioids selectively inhibit itch but not pain behaviors in the cheek model. Finally, we demonstrate that intrathecal application of kappa agonists and antagonists bidirectionally modulate itch behavior. Together these data uncover a key neuromodulatory role for dynorphin in the regulation of itch.

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TOPICAL HYPOCHLOROUS ACID (HOCL) - AN EMERGING ANTI-PRURITIC THERAPY

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Pruritus is the most common symptom seen in dermatologic disease and has a significantly negative impact upon patient quality of life. Treatment of pruritus is based on a small number of studies, including case series, which often lack appropriate controls such as double blinded or randomized study designs. This highlights the need for new evidence-based treatments. Recently, topical hypochlorous acid (HOCl) has been proposed as a treatment for pruritus. However, published research on this topic is limited and the mechanism of action has not been established. Thus, a review of the current literature on pruritus and on HOCl was conducted to ascertain potential correlations. Based on this review, we propose the following two mechanisms by which HOCl may reduce pruritus: 1) HOCl is microbicidal to cutaneous pathogens, including Staphylococcus aureus which is a common aggravating factor in atopic dermatitis; 2) HOCl is anti-inflammatory as it neutralizes interleukin (IL)-6 and leukotriene B4 (LTB4), increases inhibitory α2-macroglobulin binding to IL-2, TNF-α and IL-6, and chloraminates histamine, all of which have been implicated in the pathophysiology of itch. These findings suggest potential mechanisms by which HOCl may exert its anti-pruritic activity.

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RET+ BUT NOT CGRP+ EPIDERMAL FIBER DENSITY IS INCREASED IN A MOUSE MODEL OF DRY SKIN ITCH

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Mice scratch their cheek with a hind-limb in response to pruritogens, but wipe with their forelimb when painful compounds are applied. This allows a distinction to be made between itch- and pain-producing stimuli (Shimada & LaMotte, 2008). We combined this cheek model with a dry skin model of itch in which equal parts acetone and ether followed by water were applied to the cheek skin. Ongoing scratching (with no wiping) was significantly increased compared to the water-only control. Cheek skin was excised and total epidermal fiber density in the dry skin and control skin was assessed with immunohistochemistry. Beta-tubulin immuno-positive epidermal fiber density was increased in dry skin. This increase was present even with the use of Elizabethan collars to prevent scratching, indicating that the dry skin alone was capable of generating enhanced fiber density. Non-peptidergic epidermal fibers can be distinguished based on their expression of Ret, while CGRP is a marker of peptidergic fibers. Ret+ fibers were significantly increased in dry skin, but CGRP+ fibers were not different, suggesting that Ret+ fibers may be important for dry skin induced pruritus.

160 Duplicate.

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AUDITORY MODULATION OF ITCH

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Although it is often considered only a matter of the skin, itch is a multi-modal phenomenon. Scratching an itch does not only elicit a cutaneous sensation, but is also accompanied by visual (e.g., sight of scratching) and auditory (sound of scratching) perceptions. Here, we investigate whether such auditory stimulation alone is sufficient to induce itch. Additionally, we were interested in whether the intensity of induced itch is modulated by the proportion of high frequencies in the auditory signal. The main findings were that (*i*) listening to scratching, relative to listening to rubbing, induces itch, (*ii*) listening to scratching with a boosted high frequency component increases itch, and (*iii*) a reduction of the high frequency component of scratching sounds was associated with reduced itchiness, at least for those participants that find it generally difficult to ignore unpleasant bodily sensations. This findings highlight that social itch is induced not only by visual, but also by auditory stimuli. Additionally, modulation of itch through manipulating auditory feedback might provide new angles for the reduction of acute and chronic itch.

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THE PROBLEMATIC SENSITIVITY OF INTRADERMAL SEROTONIN AND HISTAMINE INDUCED STRACHING MODEL TO ANALGESIC DRUGS AS AN ANIMAL MODEL OF ITCH

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Although itch and pain share common pathways, they are two distinct sensations and the ideal animal model of itch should differentiate itch sensation from pain. Intradermal injection of serotonin and histamine into skin and then, the evaluation of the straching behaviour are commonly used in the estimation of antipruritic activity of drugs. In this study, we explored the effects of some clinically used analgesic drugs on serotonin and histamine-induced scratching behaviour. Serotonin (25 µg) or histamine (125 µg) was injected intradermally in a volume of 50 µl into the rostral part of skin on the back of Male Balb-C mice (23-28 gr) and scratches were counted for a 30-min observation period. Morphine (1, 3, 10 mg/kg), cannabinoid agonist CP 55,940 (0.1, 0.3, 1 mg/kg), tramadol (20, 40, 80 mg/kg), paracetamol (100, 200, 300) and diclofenac (50, 100, 200 mg/kg) were given intraperitoneally 30 min prior to pruritogen injection. All of the analgesic drugs dose dependently blocked both serotonin and histamine-induced straching behavior with the complete inhibition of their highest doses. Our results suggest that intradermal serotonin- and histamine-induced scratching models may not discriminate pain and itch sensation and give false positive results in terms of analgesic drugs.

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SPINAL NEUROTRANSMITTERS IN HISTAMINERGIC AND NON-HISTAMINERGIC ITCH

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We investigated roles for substance P (SP), gastrin-releasing peptide (GRP), and glutamate in the spinal transmission of itch in mice. In behavioral studies, we assessed effects of intrathecal (it) administration of the GRP receptor antagonist RC-3095, NK-1 antagonist L-733060, AMPA antagonist CNQX, or combinations, on hindlimb scratching elicited by intradermal (id) injection of histamine or the MrgprA3 agonist chloroquine. Each antagonist significantly attenuated chloroquine-evoked scratching; L-733060 + CNQX was more effective, and co-administration of all 3 antagonists abolished scratching. CNQX alone abolished histamine-evoked scratching. Similar results were obtained in electrophysiological recordings of dorsal horn neurons. Co-application of all 3 antagonists abolished chloroquine-evoked activity, while histamine-evoked activity was abolished by CNQX alone. We additionally employed a double-label strategy to investigate molecular markers of pruritogen-sensitive dorsal root ganglion (DRG) cells. Of chloroquine-responsive DRG cells (identified by calcium imaging), 16, 18 and 80% were immunopositive for SP, GRP and VGLUT2, respectively. Of histamine-responsive cells, 10, 17.5 and 77% were immunopositive for SP, GRP and VGLUT2, respectively. Thus, SP, GRP and glutamate each partially contribute to histamine-independent itch, while glutamate is the primary neurotransmitter involved in histamine-evoked itch. Co-application of NK-1, GRP and AMPA/kainate receptor antagonists could be a potential treatment for chronic itch.

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SCRATCHING INHIBITS SEROTONIN-EVOKED RESPONSES OF RAT DORSAL HORN NEURONS IN A SITE- AND STATE-DEPENDENT MANNER

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Itch triggers scratching to remove parasites or other invasive stimuli. Scratching suppresses itch sensation by inhibiting pruritogen-evoked responses of dorsal horn neurons. We investigated if scratching differentially affects spinal neuronal activity elicited by pruritic vs. algesic stimuli, and if inhibition depends on the location of scratching. We recorded from rat superficial lumbar dorsal horn neurons that responded to intradermal (id) microinjection of serotonin (5-HT). During the response to 5-HT, scratch stimuli were delivered at (on-site), and up to 30 mm away from (off-site), the id injection site. Off-site scratching significantly attenuated firing, followed by recovery. During on-site scratching, neuronal activity was further increased, followed by a significant post-scratch decrease in firing. Most neurons also responded to mustard oil (AITC). Off-site scratching had no effect on AITC-evoked firing, while on-site scratching further increased neuronal firing with no post-scratch decrease. Scratching exerts a state-dependent inhibitory effect on responses of spinal neurons to pruritic but not algesic stimuli. On-site scratching first excited neurons followed by inhibition, consistent with previous studies. Off-site scratching immediately inhibited pruritogen-evoked activity. This latter effect may account for the suppression of itch sensation by scratching at a distance from the site of the itchy stimulus.

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BLOCKING OF INTRADERMAL SEROTONIN-INDUCED SCRATCHING BY A POTENT INHIBITOR OF BOTH FATTY ACID AMIDE HYDROLASE AND MONOACYLGLYCEROL LIPASE OR BY AN IRREVERSIBLE INHIBITOR OF MONOACYLGLYCEROL LIPASE

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Endocannabinoid system has been described in the skin. The mostly characterized endocannabinoids, anandamide and 2-arachidonyl glycerol are degraded by fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively. It has been reported previously that FAAH inhibitors displayed antipruritic effect in some animal models. The involvement of monoacylglycerol lipase on pruritic process has not been

investigated yet. In this study, we examined the antipruritic efficacy of selective dual inhibitors of FAAH and MAGL, JZL195 and MAGL inhibitor JZL184 on serotonin induced scratching models in female Balb-C mice. Serotonin (25 µg) was injected intradermally in a volume of 50 µl into the rostral part of skin on the back of mice and scratches were counted for a 30-min observation period after injection. JZL195 (5, 10, 20 mg/kg) and JZL184 (10, 20, 40 mg/kg) were given intraperitoneally 3 h prior to serotonin injection. Both of JZL195 and JZL184 dose dependently blocked serotonin -induced scratching behavior with the complete inhibition of their highest doses. These findings provide evidence that both of FAAH and MAGL represent novel targets for antiprutitic effects and dual inhibitors of FAAH and MAGL or MAGL inhibitors may be promising drugs in the treatments of pruritus.

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URAEMIC PRURITUS DECREASES QUALITY OF LIFE IN HAEMODIALISIS PATIENTS

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Uraemic pruritus is still an important clinical problem in haemodialysis patients. The aim of this study was to evaluate the impact of uraemic pruritus on quality of life and depressive symptoms in cohort of haemodialysis patients with end-stage renal disease. A total of 200 haemodialysis patients were included to the study. The prevalence of uraemic pruritus was 38%. The haemodialysis patients with uraemic pruritus had significantly lower health-related quality of life, assessed with SF-36 questionnaire compared to haemodialysis patients without uraemic pruritus. 64.5% of patients with uraemic pruritus had impaired skin-related quality of life, evaluated with DLQI. The impairment of quality of life was correlated with intensity of uraemic pruritus, assessed with VAS and 4-item itch questionnaire. Uraemic pruritus more prominently affected female compared to male haemodialysis patients. Depression significantly correlated with quality of life and severity of depressive symptoms was associated with the intensity of uraemic pruritus. This study underscores that uraemic pruritus should be regarded as severe complication among haemodialysis patients.

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URAEMIC PRURITUS IN CHILDREN

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The literature data on uraemic pruritus in children is very limited. The aim of this study was to evaluate the frequency and severity of pruritus and skin dryness in children with chronic renal disease (CKD). The study included 103 children: 72 with CKD stage 3-5 and 31 patients with isolated primary nocturnal enuresis as a control group. Among children with CKD there were 34 on dialysis and 38 treated conservatively. Pruritus in children with CKD was found in 20.8% of cases. In the group of patients treated conservatively pruritus was observed in 18.4% of patients, and among dialysis in 23.5%. Xerosis was more commonly found in children with pruritus (66.7%) compared to those without pruritus (50.9%). Xerosis was more severe in children with pruritus than without pruritus. The problem of dry skin was identified more frequently in patients on dialysis (67.6%) than conservative treatment (42.1%). Dry skin is a major concern of children with CKD, intensifying as the disease progresses. Dry skin may play an important role in pathogenesis of pruritus in children with CKD, which is shown by higher incidence of dry skin and a greater severity in children with pruritus compared to those without pruritus.

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ANTI-PRURITIC EFFECTS OF NEUROTROPIN IN NC/NGA MICE WITH ATOPIC DERMATITIS-LIKE SYMPTOMS

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Neurotropin (NTP) is an anti-allergic drug. Although clinical trials have demonstrated the anti-pruritic effects of NTP, the mechanisms by which this agent exerts anti-pruritic activities remain unknown. Using acetone-treated dry skin model mice, we assessed the effects of NTP injection on epidermal hyperinnervation and the expression of epidermal axonal guidance molecules. Epidermal hyperinnervation was significantly reduced in the NTP-treated group compared with the controls. In addition, increased expression of semaphorin 3A mRNA was found in the epidermal sheets of NTP-treated group. These results suggested that the anti-pruritic effects of NTP were due to its suppression of epidermal hyperinnervation. Utilizing a human atopic dermatitis model, we examined the effects of NTP on scratching, epidermal hyperinnervation and other pathological conditions, such as number of infiltrating cells and epidermal thickness. NTP treatment significantly reduced the number of scratching episodes compared with saline treatment. This presentation will describe these results and discuss the anti-pruritic effects of NTP.

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