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5th International Workshop for the Study of Itch

The official workshop of the International Forum for the Study of Itch (IFSI)

October 25–28, 2009
Chinzan-so, Tokyo, Japan

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Contents of this Abstract book

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SUNDAY, OCTOBER 25, 2009

15:00–17:00 IFSI-Board Meeting of Directors: Plaza 4F 'Orchid' (only for IFSI-board directors)
17:00– Registration: Plaza 4F Lobby
19:00–21:00 Welcome Reception: Plaza 1F 'Galaxy'

MONDAY, OCTOBER 26, 2009

7:30–8:00 **Breakfast Box Pick-Up: Plaza 4F 'Jupiter'**

8:00-8:05 **Opening Remark**s, *Kenji Takamori, Sonja Ständer*

8:05-9:05 **Breakfast Symposium of IFSI-SIG and National Eczema Association: «Itch Scoring in Clinical Trials» (OP01–04)**
Chairs: Toshiya Ebata, Sonja Ständer, Jacek Szepietowski
8:05-8:15 Overview of itch measurements, *Toshiya Ebata*
8:15-8:25 Special Interest Group (SIG): Measurement of itch in clinical trials, *Sonja Ständer*
8:25-8:35 Visual analogue scale as a validated assessment of pruritus intensity, *Adam Reich*
8:35-8:45 Patient reported outcomes: Quality of life and patient benefit index, *Matthias Augustin*
8:45-8:55 General discussion between chairpersons and audience
8:55-9:05 Final conclusions and determination of next steps, *Jacek Szepietowski*

9:15-9:55 **New Clinical Aspects and Concepts of Itch and Itchy Diseases (OP05–07)**
Chairs: Jeffrey Bernhard and Sonja Ständer
9:15-9:30 What is brachioradial pruritus? *Sonja Ständer*
9:30-9:45 Itch sui generis, *Jeffrey Bernhard*
9:45-9:55 Psychopathological tactile phenomena mimicking itch (to the problem of qualification in dermatological practice), *Andrey Lvov*

9:55-10:45 **Epidemiology of Itch (OP08–11)**
Chairs: Yoshiki Miyachi, Elke Weisshaar
9:55-10:10 Prevalence of atopic dermatitis in Japan, *Masutaka Furue*
10:10-10:25 The epidemiology of chronic itch, *Elke Weisshaar*
10:25-10:35 National epidemiological study in Germany: Pruritus in a cohort of 11,700 employees, *Christine Blome*
10:35-10:45 Multidimensional database for pruritus patients – Statistical evaluation of clinical characteristics, *Tobias Lotts*

10:45-11:15 **Coffee Break & Poster Discussion (PC01–22)**

11:15-12:20 **Brain-Imaging of Itch (OP12–16)**
Chairs: Kazuhiko Yanai and Gil Yosipovitch
11:15-11:30 What can fMRI tell us about the central representation of itch and its modulation? *Clemens Forster*
11:30-11:45 Temporal aspect of the brain mechanism of itch: Human EEG and MEG studies, *Hideki Mochizuki*
11:45-12:00 Imaging of chronic itch and scratch and its challenges, *Gil Yosipovitch*
12:00-12:10 PET study of brain activation following histamine-induced itch: Central modulation with a high distraction task, *Laure Bergeret*
12:10-12:20 A tale of two itches: Common features and notable differences in brain activation revealed in a comparative fMRI study of cowhage and histamine induced itch, *Alexandru Papoiu*

12:30-13:40 **Luncheon Seminar: «Atopic Dermatitis» (OP17–18)**
Chair: Jeffrey Bernhard
12:40-13:10 Neural and inflammatory aspects of itch responses in atopic dermatitis: New action mechanism of anti-histaminic drug on mite antigen-induced skin lesions in NC/Nga mice, *Ichiro Katayama*
13:10-13:40 Serine protease - PAR2 signaling of permeability barrier homeostasi, *Peter Elias*

13:50-15:15 **Neural Mechanisms of Itch – Part 1: Rodent Studies (OP19–25)**
Chairs: Earl Carstens and Yasushi Kuraishi
13:50-14:05 Sphingosylphosphorylcholine and itch, *Tsugunobu Andoh*
14:05-14:20 Cellular basis of itch sensation, *Zhou-Feng Chen*
14:20-14:35 Itch sensitization in rodent models, *Earl Carstens*
14:35-14:45 Enhanced scratching in a mouse model of chronic dry skin itch, *Tasuku Akiyama*
14:45-14:55 Ethanol aggravates itch-related scratching via central depressant actions in hairless mice with atopic dermatitis, *Masanori Fujii*
14:55-15:05 Oral administration of dihomo-gamma-linolenic acid prevents itch in atopic NC/NgaTnd mice through PGD1 production, *Akane Tanaka*
15:05-15:15 Flaky tail mouse as a possible model of atopic dermatitis: Pruritus-associated response induced in flaky tail mouse, *Catharina Moniaga*

15:15-15:45 **Coffee Break & Poster Discussion (PB01–21)**

15:45-16:30 **Neural Mechanisms of Itch – Part 2: Other Animal Studies (OP26–28)**
Chairs: Matthias Ringkamp and Martin Schmelz
15:45-16:00 Primary afferents and the sensation of itch, *Richard Meyer*
16:00-16:15 Studies of pruriceptive and nociceptive responses of spinothalamic tract (STT) neurons in monkeys, *Glenn Giesler*
16:15-16:30 Similar mechanisms of sensitization in itch and pain? *Martin Schmelz*

16:30-17:35 **Neural Mechanisms of Itch – Part 3: Human Studies (OP29–33)**
Chairs: Akihiko Ikoma and Robert LaMotte
16:30-16:45 Neurophysiological and psychophysical studies on histaminergic and non-histaminergic itch, *Hermann Handwerker*
16:45-17:00 Neuropathic itch: Insights from patients and rat models, *Anne Oaklander*
17:00-17:15 Psychophysical studies of itch in humans: Implications for neural coding, *Robert LaMotte*
17:15-17:25 The new approach to studying neurophysiological mechanisms of itch: Evoked potentials to electrical and thermal stimulation in patients with atopic dermatitis, *Dmitry Romanov*
17:25-17:35 Mechanically evoked itch in humans, *Akihiko Ikoma*

18:00 **Departure for Tokyo Night Tour «Yakatabune Cruise»: Plaza 3F Main Entrance**

TUESDAY, OCTOBER 27, 2009

7:30–8:00 **Breakfast Box Pick-Up: Plaza 4F 'Jupiter'**

8:00–8:45 **Breakfast Seminar: «Psychotherapy for Itch» (OP34)**

Chair: Hermann Handwerker

Self-hypnosis training for symptom management: Applications for pain and itch, *Mark Jensen*

8:55–10:30 **Skin Neurobiology (OP35–41)**

Chairs: Martin Steinhoff and Makoto Tominaga

8:55–9:10 Inhibition of mouse scratching behavior by tacrolimus and its mechanisms, *Naoki Inagaki*

9:10–9:25 Transient receptor potential vanilloid 3 (TRPV3) has a role in the development of itchy dermatitis, *Takeshi Yoshioka*

9:25-9:40 Role of proteinase-activated receptors and peptidases in skin inflammation and pruritus, *Martin Steinhoff*

9:40-9:55 TRP channel functions in the skin keratinocytes, *Makoto Tominaga*

9:55–10:10 IL-31: An important player in the scene of itch, *Ferda Cevikbas*

10:10–10:20 Artemin is expressed in substance P-treated dermal fibroblasts, and contribute to the peripheral nerve fiber sprouting, *Hiroyuki Murota*

10:20–10:30 Topical cholecytokinin depresses itch-associated scratching behavior in mice, *Shoko Fukamachi*

10:30–11:00 **Coffee Break & Poster Discussion (PB01–21)**

11:00–11:50 **Opioids and Itch (OP42–45)**

Chairs: Paul Bigliardi and Kenji Takamori

11:00–11:15 The role of skin opioid receptor system in itch, *Mei Bigliardi-Qi*

11:15–11:30 Differential modulations of itch scratching by endogenous opioid peptides in the monkey spinal cord, *Mei-Chuan Ko*

11:30–11:40 Brain opioid receptor responses to psychological stress in atopic dermatitis model mice, *Hiroo Amano*

11:40–11:50 Implications for peripheral opioid systems to pruritus, *Mitsutoshi Tominaga*

12:00–12:55 **Luncheon Seminar «Animal Model of Atopic Dermatitis» (OP46)**

Chair: Gil Yosipovitch

12:10–12:55 Update on NC/NgaTnd mice as an atopic dermatitis model, *Hiroshi Matsuda*

13:05–14:15 **Chronic Itch – Part 1: Intractable Itch (OP47–OP51)**

Chairs: Torello Lotti and Jacek Szepietowski

13:05–13:20 Intractable itch in terminal care, *Zbigniew Zylicz*

13:20–13:35 Neuropeptidergic intractable itch: Problems and solutions, *Torello Lotti*

13:35–13:50 Pruritus in psoriasis: An update, *Jacek Szepietowski*

13:50–14:05 Autotaxin is a potential mediator of cholestatic pruritus, *Andreas Kremer*

14:05–14:15 Uremic pruritus: Bilateral symmetry and itch-associated morbidity, *Dawn McGuire*

14:15–15:30 **Chronic Itch – Part2: New Therapeutic Perspectives (OP52–57)**

Chairs: Alan Fleischer and Thomas Mettang

14:15–14:30 Serum concentrations of substance P are increased in cholestasis: Potential clinical implications, *Nora Bergasa*

14:30–14:45 Therapeutic strategies in chronic pruritus with systemic disease, *Thomas Mettang*

14:45–15:00 Therapeutic advances in treating itch, *Alan Fleischer*

15:00–15:10 Results of a clinical study featuring the sensory evaluation, on humans, of the antipruritic effect of a topical superoxide dismutase, *Christian Diehl*

15:10–15:20 A randomized, multicenter trial of topical tacrolimus for treatment of pruritus in patients with atopic dermatitis, *Satoshi Takeuchi*

15:20–15:30 Efficacy of sweat-antigen-inactivating spray on itching of patients with atopic dermatitis, *Hajime Shindo*

15:30–16:00 **Coffee Break & Poster Discussion (PC01–22)**

16:00–17:05 **Psychology and Psychiatry in Itch (OP58–62)**

Chairs: Masutaka Furue and Uwe Gieler

16:00–16:15 Psychogenic pruritus, *Laurent Misery*

16:15–16:30 Psychosomatic aspect and itch in patients with atopic dermatitis, *Makoto Hashiro*

16:30–16:45 Psychology of itch – Somatoform pruritus, *Uwe Gieler*

16:45–16:55 A multidisciplinary training programme for patients with chronic pruritus, *Uwe Matterne*

16:55–17:05 Suicidal ideation in itch, *Florence Dalgard*

17:05–17:50 **IFSI General Assembly: Plaza 4F 'Jupiter'**

19:00–21:00 **Congress Banquet: Hotel 1F 'Ball Room'**

WEDNESDAY , OCTOBER 28, 2009

8:00 **Breakfast Box Pick-Up & Departure: Hotel 3F**

12:00–13:00 **Lunch in Nikko**

13:00–16:30 **Sightseeing at 'Nikko Toshogu' Shrine**

17:30–18:30 **Satellite Symposium in Nikko "Opioid Kappa and Itch" (OP63–65)**

Chairs: Paul Bigliardi and Kenji Takamori

17:30–17:50 Opioids and itch: Central and peripheral mechanisms, *Martin Schmelz*

17:50–18:10 Pharmacological properties of nalfurafine, a novel antipruritic and kappa-opioid receptor agonist, *Kaoru Nakao*

18:10–18:30 Effect of a novel kappa receptor agonist, nalfurafine, for severe itch in 337 hemodialysis patients: Phase III, randomized, double-blind, placebo-controlled study, *Hiroo Kumagai*

19:00–21:00 **Farewell Dinner at Nikko Kanaya Hotel**

POSTERS

PB01: Evaluation of residual sedative effect of antihistamines by measuring central histamine H_1 receptor occupancy using 11C-doxepin-PET. *Kazuhiko Yanai, Dongying Zhang, Tashiro Manabu, Katsuhiko Shibuya*

PB02: Olopatadine hydrochloride inhibits scratching behavior induced by a proteinase-activated receptor 2 agonist in mice. *Ayumi Yoshizaki, Shinichi Sato*

PB03: The effect of Yokukansan on atopic dermatitis-like lesions in socially isolated NC/Nga mice. *Naoko Funakushi, Ju Jiang, Takuji Yamaguchi, Takatoshi Kuhara, Shigaku Ikeda*

PB04: Development of a novel mouse atopic dermatitis model induced by mite fecal antigen. *Hirotaka Yamashita, Yoshihiro Miyamoto, Hiroyuki Tanaka, Hiroichi Nagai, Naoki Inagaki*

PB05: Inhibitory transmitters mediating scratch-evoked inhibition of spontaneously active spinal dorsal horn neurons in a mouse model of chronic dry skin itch. *Tasuku Akiyama, Mirela Iodi Carstens, Earl Carstens*

PB06: Distinct scratching and wiping behaviors elicited by intradermal injection of pruritogens or algogens into the cheek of mice and μ-opioid modulation. *Tasuku Akiyama, Mirela Iodi Carstens, Earl Carstens*

PB07: Excitation of mouse superficial dorsal horn neurons by histamine and/or PAR-2 agonist: potential role in itch. *Tasuku Akiyama, Mirela Iodi Carstens, Earl Carstens*

PB08: Itch-inhibitory system mediated by activation of α-adrenoceptors in the spinal cord. *Yoshikazu Gotoh, Tsugunobu Andoh, Yasushi Kuraishi*

PB09: Development of atopic dermatitis model and effects of Actinidia extract on dermatitis in NC/Nga mice. *Seong-Jin Jo, Young Hyun Joo, Ji Youn Kim, Oh Sang Kwon, Kyu Han Kim*

PB10: Scratching and spinal c-Fos expression in mice peripheral or central itch models. *Hiroshi Sekiyama, Masakazu Hayashida, Kazuo Hanaoka, Toshinobu Sumida, Yoshitsugu Yamada*

PB11: Antipruritic effect of dexmedetomidine or clonidine is mediated by spinal α_{2A}-adrenoceptors. *Hiroshi Sekiyama, Masakazu Hayashida, Kazuo Hanaoka, Toshinobu Sumida, Yoshitsugu Yamada*

PB12: Cowhage spicules vigorously activate a subpopulation of Ad nociceptors in monkey. *Matthias Ringkamp, Raf J. Schepers, Lisa M. Johanek, Tim V. Hartke, Beom Shim, Jasenka Borzan, Richard A. Meyer*

PB13: Histamine-induced itch does not depend on the activation of polymodal nociceptors. *Christian Menzer, Roman Rukwied, Marcus Schley, James Blunk, Otilia Obreja, Justus Benrath, Martin Schmelz*

PB14: Immunohistochemical localization and expression levels of transient receptor ion channels (TRP) in human skin and patients with pruritic diseases. *Jamison D. Feramisco, Matthias Sulk, Joerg Buddenkotte, Akihiko Ikoma, Ferda Cevikbas, Stephan Seeliger, Johannes Voegel, Jerome Aubert, Philip LeBoit, Allan Basbaum, David J. Julius, Martin Steinhoff*

PB15: Role of Cav1.2 L-type calcium channel in xenobiotic metal induced mast cell activation. *Koremasa Hayama, Yoshihiro Suzuki, Mayumi Murai, Toshio Inoue, Toyoko Ochiai, Tadashi Terui, Chisei Ra*

PB16: Epidermal nerve density is modulated by keratinocytes-produced anosmin-1. *Suhandy Tengara, Mitsutoshi Tominaga, Atsuko Kamo, Kenichi Taneda, Osamu Negi, Hideoki Ogawa, Kenji Takamori*

PB17: Decreased expression of semaphorin 3A in the lesional skin of psoriasis with itch. *Ken Zen Kou, Fumio Nakamura, Michiko Aihara, Takeshi Kanbara, Keishi Chin, Yoji Nagashima, Yoshio Goshima, Zenro Ikezawa*

PB18: Cathepsin S is an endogenous cysteine protease, elicits itch, and signals via protease-activated receptors. *Ethan A Lerner, Steven G. Shimada, Paul Sikind, Robert H. LaMotte, Vemuri B. Reddy*

PB19: Acidic pH induces matrix metalloproteinase (MMP)-9 (gelatinase b) expression and caspase-3/7 activity from keratinocyte in culture. *Takashi Kobayashi*

PB20: The basis of topical superoxide dismutase antipruritic activity. *Christian Diehl*

PB21: Identification of lysophosphatidic acid as neural activator in blood of pruritic cholestatic patients. *Andreas E. Kremer, Job J. Martens, Wim Kulik, Catherine Williamson, Jurate Kondrackiene, Ulrich Beuers, Ronald P.J. Oude Elferink*

PC01: Assessment of pruritus intensity: Correlation between visual analogue scale, numeric rating scale and verbal rating scale in patients with chronic pruritus. *Ngoc Quan Phan, Sonja Ständer*

PC02: How to measure itch intensity? A systematic literature review. *Christine Blome*

PC03: Patients with chronic pruritus treated in a specialized itch clinic: Results and experiences. *Marion Buettner, Robert Ofenloch, Elke Weisshaar*

PC04: Estimating the prevalence of chronic itch: How common is the symptom? *Uwe Matterne, Christian Apfelbacher, Tamara Strassner, Adrian Loerbroks, Marion Buttner, Elke Weisshaar*

PC05: Characteristics of pruritus among Turkish patients attending a Dermatology clinic. *Ekin Savk, Meltem Uslu, Arzu Gorgulu Eraslan, Neslihan Sendur, Goksun Karaman*

PC06: High prevalence of pruritus associated with poor outcome is still common in hemodialysis patients. *Björn Wikström, Doug S. Fuller, Fritz K. Port, Ronald L. Pisoni*

PC07: Comparison between perceived itch induced by skin prick-tests with histamine or codeine. *Jennifer Theunis, David Black, Arnaud Degouy, Anne-Marie Schmitt, Laurent Misery*

PC08: Evaluation of psoriatic itch by epidermal nerve density and opioid receptor levels. *Kenichi Taneda, Mitsutoshi Tominaga, Osamu Negi, Atsuko Kamo, Suhandy Tengara, Kenji Takamori*

PC09: Pruritus and psoriasis: Clinical study. *Mariya Katsina*

PC10: Pruritus and work ability in psoriatic patients. *Izabela Zimolag, Adam Reich, Jacek Szepietowski*

PC11: Clinical observations on generalized pruritus: A retrospective study. *Hyun Jung Lim, Jae Hun Jun, Jae Chul Lee, Byung Soo Kim, Weon Ju Lee, Seok-Jong Lee, Do Won Kim*

PC12: Quality of life in chronic pruritus measured with ItchyQoL. *Scott W. Dunbar, Sallyann M. Coleman King, Loebat Kamalpour, Ricardo L. Berrios, Nikki D. Hill, Emir Veladar, Suephy C. Chen*

PC13: The role of TARC and itch in patients with atopic dermatitis**.** *Koichiro Nakamura, Kojiro Takiguchi, Tetsuya Tsuchida*

PC14: Targeting the neurokinin receptor 1 as a new antipruritic strategy: Results of a case series with aprepitant. *Sonja Ständer, Dorothee Siepmann, Thomas A. Luger*

PC15: Antipruritic potency of the triterpene betulin in patients with chronic pruritus. *Ngoc Quan Phan, Dorothee Siepman, Matthias Augustin, Melanie N. Laszczyk, Thomas A. Luger, Sonja Ständer*

PC16: Successful treatment of therapy resistant pruritus in lichen amyloidosis with menthol. *Martha Froehlich, Alexander Enk, Thomas L Diepgen, Elke Weisshaar*

PC17: Functional itch and mental disorders in dermatological clinic (results of pilot study). *Dmitry V. Romanov, Andrey Lvov*

PC18: Aquagenic pruritus in polycythemia rubra vera patients – An observation of 2 cases over a period of 2 years. *Michael Haeberle*

PC19: Double dose of cetirizine is effective for urticaria patients hypo-responsive to the ordinary dose. *Yukari Okubo, Masashi Yamazaki, Ryoji Tsuboi*

PC20: Causes of Chronic Pruritus: Patient Perceptions. *Anja Bathe, Elke Weisshaar*

PC21: Stress management alleviates atopic pruritus. *Toshiharu Fujiyama, Hideo Hashizume, Masahiro Takigawa*

PC22: Depression-related pruritus: A clinical study. *Przemyslaw Pacan, Magdalena Grzesiak, Adam Reich, Jacek Szepietowski*

ABSTRACTS: Oral Presentations (OP01-OP65)

OP01 OVERVIEW OF ITCH MEASUREMENTS

Toshiya Ebata
Chitofuna Dermatology Clinic, Tokyo, Japan

Since itch is a subjective symptom and capricious by nature it is difficult to measure. But quantitative evaluation of itch is necessary for assessing the treatment efficacy of antipruritics, judging the severity of pruritic dermatoses, and elucidating the mechanisms of itch. For the direct evaluation of itch we have to rely on the patients' own rating of their subjective symptoms. In the process of scoring the itch sensation, some scales are used. They are categorical scales (eg. behavioral rating scale), numerical rating scales (eg. 11-point intensity interval scale) and the visual analogue scale (VAS). Among these VAS has been used most commonly. It is said to be simple, accurate and universally accepted. Itch has multidimensional aspects (eg. severity, duration, frequency, spatial distribution, quality). The assessment of severity, frequency and duration seems to be essential for its quantification. For this purpose a computer-based analyzing system, which consists of a handy data logger, an interface to connect to the personal computer and a software for storage, analysis and presentation of data, measures the product of itch intensity and duration continuously with sufficient accuracy. Scratching during sleep is measured as an indirect correlate of itch. Unlike scratching during the daytime, nocturnal scratching is considered to be uninfluenced by psychosocial factors. An infrared video camera and a wrist activity monitor are used to measure nocturnal scratching for the research purpose. Though there is criticism that the amount of scratching may not reflect the true state of itch, getting the objective values is useful especially in pediatric patients who cannot express the extent of itch. Brain imaging techniques such as fMRI are recently developed to observe the central process of itch and are expected to measure itch directly and objectively in future.

OP02 SPECIAL INTEREST GROUP (SIG): MEASUREMENT OF ITCH IN CLINICAL TRIALS

Sonja Ständer
Neurodermatology and Competence Center Pruritus, Department of Dermatology, University of Munster, Germany

Chronic pruritus is a multidimensional and subjective symptom. Patients report next to individual pruritus intensity, quality, localization, duration, course, and scratching behaviour also interindividual variations in impact on quality of life, reduction of sleep time and psychosomatic consequences. Most of these factors temporally influence the itch severity, especially the itch intensity. In clinical trials, the efficacy of new substances is measured by the relief of the symptom, i.e. the regression of the pruritus intensity. To date, the most commonly used tool for self-report of itch intensity is the visual analogue scale (VAS). However, the application of the VAS is critical since it is influenced by several parameters including stress, anger and current mood. Depending on the time-point of a study visit pruritus intensity may vary and thus, the VAS may not reflect the actual regression of the symptom. This poses a major source of measurement error due to inconsistent study data and reduced data sensitivity. Therefore, the development and validation of additional tools is necessary. Currently, several new interesting tools are under development or already validated. For example, the Eppendorf Itch Questionnaire (EIQ), Questionnaire for coping with itch ("JKF"), pruritus-specific quality-of-life questionnaire (ItchyQoL) and Patient Benefit Index for pruritus patients (PBI-P) are already available. The development of new robust assessment tools to monitor the improvement of several pruritus parameters such as e.g. dynamic pruritus score (measuring quantitative itch reduction), improvement of sleep time or regression of pruritus related-anxiety and depression is most desirable. This SIG aims to give recommendations for the use of VAS in clinical trials and application of additional and new tools.

OP03 VISUAL ANALOGUE SCALE AS A VALIDATED ASSESSMENT OF PRURITUS INTENSITY

***Adam Reich**, Monika Heisig, Jacek C. Szepietowski*
Wroclaw Medical University, Department of Dermatology, Venreology and Allergology, Wroclaw, Poland

Pruritus is a common symptom of numerous skin diseases. However, the assessment of its intensity remains a challenge. The aim of the study was the validation of visual analogue scale (VAS) as an instrument for pruritus evaluation. One hundred patients aged between 18 and 83 years (mean 56.9±15.9), suffering from pruritic skin diseases were included into the study. All patients were asked to assess the intensity of pruritus using the horizontal and vertical VAS (0: no pruritus, 10: the most intensive pruritus), 10-point verbal (numeric) scale as well as 4-point self-assessment scale (mild, moderate, severe and very severe pruritus). The intensity of pruritus was assessed as mild by 24%, moderate by 34%, severe by 25% and very severe by 17% patients. The severity of pruritus according to horizontal VAS ranged between 0.4 and 10 points (mean 5.5±3.0 points), according to vertical VAS between 0.3 and 10 points (mean 5.5±3.1 points), and according to 10-point verbal scale between 0.5 and 10 points (mean 5.9±2.6 points). A highly significant correlation was found between results obtained by horizontal and vertical VAS (R=0.95; $p<0.001$), slightly less prominent correlation was observed between 10-point verbal scale and both VAS scales (R=0.84–0.85; $p<0.001$). Regarding the 4-point self assessment scale, the highest correlation was found with 10-point numeric scale (R=0.8, $p<0.001$), followed by horizontal (R=0.7, $p<0.001$) and vertical VAS (R=0.68, $p<0.001$). Furthermore, the highest convergence of results between 4-point self-assessment scale and horizontal VAS was obtained for following cut points of VAS: mild pruritus: <3 points, moderate pruritus: ≥3<7 points, severe pruritus: ≥7<9 points, very severe pruritus: ≥9 points (R=0.71, $p<0.001$). 10-point verbal scale seems to reflect in the highest degree the subjective feeling of pruritus severity. Our study is the first one trying to suggest the cut points of VAS according to the pruritus intensity.

OP04 PATIENT REPORTED OUTCOMES: QUALITY OF LIFE AND PATIENT BENEFIT INDEX

***Matthias Augustin**[1], Christine Blome[2], Sonja Ständer[3]*
[1]Department of Dermatology, University Clinics of Hamburg, [2]Department of Dermatology, University Clinics of Hamburg, CV Derm, [3]Department of Dermatology, University of Munster, Germany

Background: Today, cost reimbursement of drugs requires giving empirical evidence of therapeutic benefit in, for exam-

ple, Australia, Canada, France, and Great Britain. In Germany, regulatory agencies explicitly stated that patient benefit has to be assessed from the patient's perspective. Most commonly, patient benefit is measured as change in quality of life in clinical and health services studies. This method, however, neglects the individual importance that different treatment objectives have, because it does not weigh treatment benefits according to the patients' preferences. **Aims:** Development and validation of a questionnaire on patient-relevant benefit in the treatment of pruritus. **Methods:** Fifty patients with pruritus provided information on their impairments due to pruritus and their treatment objectives. Based on the results, the two-page questionnaire "Patient Benefit Index for pruritus" (PBI-P) was developed. The PBI-P assesses patients' treatment needs before therapy and patient benefit after therapy. It was tested for feasibility by 36 patients. Afterwards, it was validated in a sample of 100 patients who filled in both PBI and Dermatology Life Quality Index (DLQI) before and after therapy. **Results:** The instrument was feasible in clinical practice; there were few missing values. The needs questionnaire proved reliable with Cronbach's alpha of 0.93. The PBI-P was convergently valid with respect to reduction of pruritus and dermatology-specific quality of life. Mean DLQI improved from 8.8±6.8 at therapy onset to 7.2±6.2 after therapy. **Conclusions:** The PBI for pruritus seems to be a feasible, reliable, and valid instrument for recording patient-reported benefit. There was striking impairment in the patients' quality of life.

OP05 WHAT IS BRACHIORADIAL PRURITUS?

Sonja Ständer[1], *Esther Pogatzki-Zahn*[2], *Ulrike Raap*[3], *Britta Schuhknecht*[1], *Dorothee Siepmann*[1], *Gudrun Schneider*[4], *Martin Marziniak*[5]

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Brachioradial pruritus (BP) is a rare form of chronic localized itching usually occurring at the lower arms. In recent case reports BP is defined as neuropathic pruritus and attributed to spinal cord compression. We investigated 40 patients (27 women, 13 men, 27–77 years; mean 60.2±10.32 years) with localized pruritus of dorsolateral aspect of both arms. Next to clinical examination, we investigated cutaneous NGF level and intraepidermal nerve fiber density (IENF), function of C- and A-fibers by quantitative sensory testing (QST) according to a standardized protocol and spinal cord anatomy by magnet resonance tomography. 38/40 (95.0%) patients reported on itching, burning and/or stinging while 2/40 (5.0%) patients described pure itching. Mean IENF was within the normal range, i.e., in the pruritic skin 14.51 fibers/mm. Immunostaining for NGF revealed an increased number of NGF positive nerves in lesional skin compared to healthy subjects ($p<0.001$). Further, the number of NGF positive nerves with a diameter greater than 15 µm was higher in brachioradial pruritus compared to controls ($p<0.001$). Quantitative sensory testing revealed heterogenous results concerning threshold for warmth and cold sensations including heat and cold pain thresholds. In single patients, also sensation for pressure pain thresholds was altered. However, a consistent pattern of decreased (or increased) function within a nerve fiber class was not detected. Magnet resonance imaging showed that 20/40 patients had a stenosis of intervertebral neuroforamen with compression of nerve structures, 17/40 had a protrusion of cervical disc with dura mater impression and 4/40 had spinal canal compression. Together, 80% of patients showed spinal cord abnormalities leading to circumscribed pruritus. Presence of normal nerve fiber density underlines the hypothesis of extra-cutaneous origin of pruritus. Increased NGF levels may reflect scratching-related changes.

ITCH SUI GENERIS OP06

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Itch sui generis (ISG), pruritus sui generis, and pruritus idiosyncratica* are three interchangeable terms used to describe an individual's "own little itch." ISG usually recurs intermittently at the same site(s). Ordinarily, no primary skin lesions or visible changes can be detected. According to dictionary.com, sui generis describes something that is "the only example of its kind; constituting a class of its own; unique." Many now well known pruritic curiosities, such as notalgia paresthetica and brachioradial pruritus, were initially thought to be unique, then rare, and then rather common, thereby tracing a path from sui generis to quotidian. (This sequence provides one of several good arguments for the importance of case reports.) Other curiosities, such as nasal itch evoked by flossing the upper teeth or nasal itch as a manifestation of atypical angina, having been reported in only single patients, remain sui generis. (The nasal variant of pruritus prohibitus, as described by Huckleberry Finn, is common and therefore no longer an itch sui generis.) Over the years, I have seen a number of patients whose itches have not fit neatly into recognized diagnoses. These include a young man with an irresistible itch localized to one heel, a young woman with bilateral neuropathy in the distribution of the medial plantar nerves, a young woman with tarsal tunnel syndrome, and a good number of elderly patients with generalized pruritus of multifactorial origin. Further reflections on the existential and epistemological importance of pruritus sui generis will be presented.

PSYCHOPATHOLOGICAL TACTILE PHENOMENA MIMICKING ITCH (TO THE PROBLEM OF QUALIFICATION IN DERMATOLOGICAL PRACTICE) OP07

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The problem of qualification of psychopathological equivalents of idiopathic pruritus is highly actual. First of all, various "itch-like" psychopathological body sensations may precede autodestructive behaviour and underlie factitious dermatoses. According to our data, firstly, they refer to circumscripta hypochondria, characterized by obligatory symptomocomplex: local sensations of foreign matter in skin, as well as itch, burning and pain, accompanied by tendency to elimination of sensations by means of severe self-destruction. Secondly, polymorphous pathologic sensations in skin could be classified as hysteralgia (paroxysmal sensations of burning, crawling, pricking etc., which relieve only after obsessive scratching). These sensations always precede self-destructive behaviour in neurotic excoriations (and non-destructive behaviour in glossodynia, glossopyrosis, scalp dysaesthesia and vulvodynia)

comorbid to hysteria. In many cases psychogenic itch could be a presentation of somatoform disorder. Tactile hallucinosis (delusional parasitosis) could be associated with excoriations also. It reflects both the delirium theme and it's somatic projection. However, in the case of cenestopathies excruciating sensations localize not only in the skin, but also in the area of internal organs and these patients do not present self-destructive behaviour. On the other hand, implicated pruritus could arise in actual dermatological diseases (atopic dermatitis, eczema, psoriasis). It amplifies or reproduces preexisting itch, common for a dermatosis. Although such "superstructure" of itch develops due to psychogenic mechanisms, it requires differentiation from genuine psychogenic pruritus, developing without any somatic basis. Clinical presentations of implicated pruritus are notable for dissociation between minimal symptoms of dermatosis and great extent of complains on disturbing body sensations, as well as extraordinary fast reduction of itch (as a result of psychopharmacological treatment). Thus, a possible approach to improve classification of comorbid dermatological and psychiatric conditions is based on a syndromal paradigm, distinguishing a central "axis" of different psychopathological disorders of gradual severity (from neurotic to delusional) as a tactile coenestopatic syndromes.

OP08 PREVALENCE OF ATOPIC DERMATITIS IN JAPAN

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Atopic dermatitis (AD) is a common, chronic or chronically relapsing, severely pruritic, eczematous skin disease. The incidence of AD is generally considered to be increasing worldwide. The percentage of adolescent- and adult-type AD has also been increasing. The incidence in Japanese elementary school students was around 3% in 1981 to 1983 but increased to around 6 to 7% in the 1990s. In 2000 to 2002, the research team of Japanese Ministry of Health, Labor and Welfare performed physical examinations of 48,072 children living in Asahikawa, Iwate, Tokyo, Gifu, Osaka, Hiroshima, Kochi, and Fukuoka. They reported that national average prevalence rate of AD was 12.8% in 4-month-old children, 9.8 % in 18-month-old, 13.2 % in 3-year-old, 11.8 % in 6- to 7-year-old, 10.6 % in 12- to 13-year-old, and 8.2% in 18-year-old children. From 2001, we started a 0–6-year children cohort study in Ishigaki islands, named as Kyushu University Ishigaki Atopic Dermatitis Study (KIDS). KIDS revealed a lower prevalence (around 6%) of AD in the Ishigaki islands, located near Taiwan, compared to mainland Japan. KIDS allows us to analyze a rate of chronological improvement and onset of AD, chronological changes of serum IgE and TARC levels, risk factors, and some genetic predisposition. In this talk, I would like to try to answer some of our clinical and epidemiological questions in atopic dermatitis.

OP09 THE EPIDEMIOLOGY OF CHRONIC ITCH

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The symptom of chronic itch represents a worldwide burden in the community and in specific populations. It has been more extensively researched over the last years. Nevertheless, there are few true epidemiological studies on itch. Prevalence measures individuals affected by a disease or symptom within a particular period of time. Incidence measures the number of new individuals who contract a disease or symptom within a particular period of time. The causes of chronic itch seem to vary depending on age, ethnicity, characteristics of the regional health care system and the study population. Chronic itch is often ignored as a disease symptom in clinical studies. Research is complicated because the causes of chronic itch are frequently multifactorial, especially in the elderly. The comparability of existing studies is difficult because of differing methodology and lack of standardised measures. The symptom of itch is not only challenging to the clinician but also to the structure of the regional health system and the accessibility to specialized medical doctors. All this may explain why epidemiological research on itch has been disregarded for a long time. New data show that the symptom of itch is highly prevalent and should receive adequate attention from physicians and other health care rovier.

NATIONAL EPIDEMIOLOGICAL STUDY IN GERMANY: PRURITUS IN A COHORT OF 11,700 EMPLOYEES *OP10*

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Aims: The study aims to assess the prevalence, quality and severity of chronic itch in the German working population. **Methods:** A cross-sectional observational study was conducted on employees, aged 16-70 years, of 144 German companies from various branches. Data ascertainment in reference to pruritus was based on standardized questions. From 1/2008 to 12/2008 the questions were embedded into clinical examinations and interrogations conducted routinely for in-house cancer screening by trained dermatologists. **Results:** 11,732 persons examined (53.2% male) were suitable for analyses. Point-prevalence of pruritus (at least six weeks prior to data collection) was 16.8%. Gender differences were small (male 16.1%; female 17.5%) but prevalence rises with increasing age from 12.3% (16–30 years) to 20.3% (61–80 years) The single most localizations of pruritus were arms and legs, the whole body was affected in 16%. On a scale from 0 to 10 mean intensity of itch was rated 5.8. A quarter of the affected persons suffered from pruritus for more than 5 years. 47% did not attend a doctor due to itch; 94% had not applied any local or systemic treatment. Study participants who suffered from pruritus frequently or constantly also perceived a significantly higher intensity of itch. Chronic pruritus was more persistent in persons suffering from dermatological comorbidities, e.g. atopic eczema or psoriasis. **Conclusions:** As the age distribution of this cohort corresponds largely to the data of the general working population in Germany a broad representativeness of the findings can be assumed. Chronic itch is a prevalent symptom in the general population at working age. There is a high proportion of persons who suffer from itch – even for a long time and to a large extent – who are attending work and who are not under medical treatment. For this group a considerable extent of medical undersupply can be hypothesized.

OP11 MULTIDIMENSIONAL DATABASE FOR PRURITUS PATIENTS – STATISTICAL EVALUATION OF CLINICAL CHARACTERISTICS

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A descriptive, multidimensional database was programmed to survey the demographics, diseases and clinical characteristics of chronic pruritus patients. The database contains besides demographic data a large set of pruritus characteristics such as skin-condition, localisation, course and quality of pruritus. To date, the new installed database comprises 379 patients with chronic pruritus (176 male, 203 femal, mean age 60.1 years). Next to itch, half of the patients describe the quality of the symptom to be mixed with burning (50.9%) or stinging (43%). Warmth (19%) or cold (3.4%) sensations are rarely experienced. 50.9% of the patients feel alleviation of itch by scratching, on the other hand the itch increases through scratching in 36.9% reflecting alloknesis or turns into burning (21.1%). Nearly half the patients presented without scratch lesions (47.8%) on their first day of treatment. About 20% showed single scratch lesions and 32.5% already had multiple scratch lesions including prurigo nodularis. The itch occurs mostly at daytime (47%) or in the evening (45.4%), respectively nights (42.2%). It seldom occurs in the morning (13.5%). Pruritus trigger factors are especially pressure (38.8%) and touch (36.1%), followed by sweating (34%) and emotional stimuli (33.2%). Initially the pruritus was restricted in most patients to single areas (localized pruritus; 67.3%) which switched in the course of the disease in most patients into generalized pruritus (76.0%). Pruritus occurred on the trunk (62.8%), the arms (70.7%) and the legs (71.2%). The itch intensity was measured by the visual analog scale from 0 to 10. The intensity was rated rather strongly by the patients since the mean value was at 7.1 and the worst itch intensity in average at 8.9. The data evaluation allows a deeper understanding of the course and characteristics of chronic pruritus and the patients´ perception of the symptom.

OP12 WHAT CAN fMRI TELL US ABOUT THE CENTRAL REPRESENTATION OF ITCH AND ITS MODULATION?

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Cowhage and histamine induce itch. However, the quality of the sensations induced by the two substances and also the effects of scratching on the time course of the itch intensity and of sympathetic reflexes are somewhat different (see abstract of Handwerker et al.). It has been assumed that both agents activate different pathways and will induce different patterns of central activation. Functional MR imaging (fMRI) on itch is challenging since the respective protocol requires intermittent on- and off-cycles of a stimulus which are difficult to get with itch. Therefore, we focused on the interaction of itch and scratch. Healthy volunteers were repetitively scratched near the application site in the absence and presence of itch induced by histamine or cowhage. BOLD effects were assessed in predefined cortical and subcortical brain regions of interest. The main activation clusters were determined by contrast-analysis of the BOLD signal immediately before a scratch bout (during itch of high intensity) and a short period following it (itch relief). Clusters of significant contrasts were found in cortial and subcortical areas , namely in S1, S2, insula cortex, anterior cingulum (ACC), frontal areas, and caudate. In most of these regions the BOLD signal quickly dropped down after a 15 second scratch-bout and reached levels below baseline. Then it recovered and increased until the next scratch bout. In frontal regions and in the ACC these drops were larger during histamine itch than during cowhage itch. In S1 and S2 the recovery after the scratch bouts was quicker during the cowhage induced itch. This is in line with the lower susceptibility of cowhage itch to scratch inhibition found in the psychophysical study.

TEMPORAL ASPECT OF THE BRAIN MECHANISM OF ITCH: HUMAN EEG AND MEG STUDIES OP13

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Many researchers have investigated the brain mechanism of itch using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). Previous itch studies mainly focused on spatial aspect of the brain mechanism of itch (i.e. which brain regions are associated with itch). On the other hand, its temporal aspect (e.g. the sequence in which itch-related brain regions are activated) is still unclear. It is difficult to visualize temporal aspect of the brain mechanism of itch using PET and fMRI, since temporal resolution of these apparatuses is low. On the other hand, electroencephalography (EEG) and magnetoencephalography (MEG) can measure brain activity in the order of ms. In addition, a novel itch stimulus (electrically evoked itch) useful for EEG and MEG studies was developed recently. Thus, we investigated temporal aspect of the brain mechanism of itch using electrically evoked itch, EEG and MEG. In the EEG study, we observed that the peak latency of itch-related somatosensory evoked potential at vertex associated with the activation of the cingulate cortex was 963 sec when the itch stimuli were applied to the right wrist. In the MEG study, we observed that itch-related magnetic responses in the contralateral and ipsilateral secondary somatosensory cortex/insula (SII/insula) occurred at 740 and 785 msec, respectively, when the itch stimuli were applied to the left wrist. In addition, we also observed that itch-related magnetic response in the precuneus occurred between those in the contralateral and ipsilateral SII/insula. These findings demonstrate that high temporal resolution such as EEG and MEG is useful to investigate temporal aspect of brain mechanism of itch.

IMAGING OF CHRONIC ITCH AND SCRATCH AND ITS CHALLENGES OP14

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Research into brain imaging of itch and scratch has been focused on experimental acute itch with histamine in healthy subjects. However, there is scant information about brain processing of itch in clinical itch settings in particular in

patients with chronic itch. Chronic itch involves an intricate interplay between sensory, cognitive and emotional aspects and in most cases the pathophysiology is unknown. There are several methodological difficulties in interpreting the current brain imaging data and its relevance to clinical itch states. In this review I will critically discuss the methodological problems associated with brain imaging of clinical itch and scratching and the validity of the current models. To overcome some of these problems new models of itch induction using non histaminergic stimuli as well as different brain imaging techniques will be discussed. Several strategies will be proposed for future studies.

OP15 PET STUDY OF BRAIN ACTIVATION FOLLOWING HISTAMINE-INDUCED ITCH: CENTRAL MODULATION WITH A HIGH DISTRACTION TASK

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Introduction: PET and fMRI studies on brain activation with itch have shown this to be modulated with peripherally applied stimuli (thermal, pain), however, centrally applied stimuli may also have an effect. The aim of our work was to study the impact of a distraction task on any central modulation of the cortical network involved in the itch sensation. **Methods:** Histamine itch was induced on the right forearm in 14 healthy males aged 20–35 years. Saline was used as a control. The distraction task was an incongruent colour-word Stroop test, where subjects had to say the colour of the printed word but not read it. Four stimulus/Stroop conditions were applied 3 times with cerebral blood flow (CBF) changes being recorded for 2 min using $H_2{}^{15}O$ PET : 1) saline (S), 2) histamine (H), 3) saline + Stroop (SS), 4) histamine + Stroop (HS). After each PET scan, itching was rated verbally using a 10 cm visual analogue scale (VAS). **Results:** VAS-rated itch was low (max 2 cm) with intensity as follows: H>HS>S=SS. Contrasts between histamine and control PET CBF images without the Stroop test showed ipsilateral activation of the inferior and posterior parietal cortex and the cingular cortex. With the Stroop test there was ipsilateral activation of the insular cortex. Effective connectivity analysis showed a strong link between these 3 areas without Stroop which was attenuated with Stroop. **Conclusions:** The impact of distraction on the central response to itch perception is demonstrated as a different pattern of brain activity. Under normal conditions the itch sensation reaches the parietal cortex whereas with the distraction task it stays in the temporal and insular areas. Further work could see this approach being applied to chronic itch sufferers.

OP16 A TALE OF TWO ITCHES: COMMON FEATURES AND NOTABLE DIFFERENCES IN BRAIN ACTIVATION REVEALED IN A COMPARATIVE fMRI STUDY OF COWHAGE AND HISTAMINE INDUCED ITCH

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PET and fMRI brain imaging studies targeting neural networks underlying itch sensation have previously used histamine as the sole itch inducer. Cowhage induced itch represents a form of itch that activates a separate spinothalamic pathway and could provide further insight into its central processing. We hereby report for the first time a functional MRI Arterial Spin Labeling (ASL) study of neuronal processing of itch induced by cowhage spicules in comparison to histamine-induced itch. We also explored brain responses induced by histamine and cowhage combined in a tight sequence and then we correlated itch intensity to brain activation. Results of ASL fMRI analysis obtained in a group of 12 healthy volunteers suggested that cowhage and histamine in single application activated a core group of brain structures, while also revealing notable differences by inducing activation in distinct structures. Core areas activated by both stimuli are located in the inferior parietal, superior and middle temporal cortices, cuneus, precuneus, thalamus, PCC, precentral gyrus, ACC, paracentral lobule and secondary somatosensory cortex. Cowhage induced a notably distinct and more extensive involvement of the insular cortex, claustrum, basal ganglia, putamen, thalamic nuclei and pulvinar. Interestingly, cowhage and histamine applied alone activated subtle limbic structures like mammillary bodies, while this activation was not observed when these stimuli were combined. The combined application of histamine and cowhage produced brain activation in a more wide-spread fashion in the major areas activated by cowhage and histamine alone. Preliminary results in a subset of subjects indicated discrete subcortical structures appearing to be activated by the summation of histamine and cowhage, but not by these stimuli alone. By exploring the brain responses induced by different forms of itch, we hope the present results will provide a new angle for advancing our understanding of the cerebral processing of itch.

OP17 NEURAL AND INFLAMMATORY ASPECTS OF ITCH RESPONSES IN ATOPIC DERMATITIS: NEW ACTION MECHANISM OF ANTI-HISTAMINIC DRUG ON MITE ANTIGEN-INDUCED SKIN LESIONS IN NC/NGA MICE

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Itch, one of the characteristic aspects of atopic dermatitis (AD), is largely concerned with the severity of dermatitis by causing scratching behavior. In addition, it is a big primary factor which decreases QoL of the patients, and an important clinical issue to be solved. The skin of AD patients is in the state of hypersensitivity to itch. Histological observation of the skin reveals that the sensory nerves extend to inside the epidermis and that inflammatory cells such as mast cells exist around the nerves. Recently, the mechanism of the extension of sensory nerves and the inflammation which is related to hypersensitivity to itch has been considerably clarified. And also, related moecules so far unknown are being found, such as an epidermal growth factor amphiregulin, an axonal guidance molecule semaphorin3A, a Th2-type cytokine TSLP, and a Th2-type chemokine TARC.

AD remedy in Japan mainly uses external steroids, but anti-histamines are also used to treat itch. Anti-histamine drugs are reported to have many other effect than H1 antagonistic effect, but they are not clarified in detail. We are investigating the occurrence mechanism of itch with mite antigen-induced atopic dermatitis model i NC/Nga mice. In this speech, I outline the neural and inflammatory mechanisms of itchverified using this mice model, and also introduce the effect ofanti-histaine ru.

OP18 SERINE PROTEASE- PAR2 SIGNALING OF PERMEABILITY BARRIER HOMEOSTASIS

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Multiple signaling mechanisms are activated following barrier perturbation. These signals upregulate diverse metabolic processes that are required to normalize function. Barrier perturbations are inevitably accompanied by an elevation of stratum corneum pH, which in turn activates serine proteases (SP) in the outer epidermis. SP in turn activate PAR2, which localizes to the plasma membrane of granular cells, with 2 important cellular outcomes: 1) blockade of lamellar body (LB) secretion; and 2) acceleration of terminal differentiation; i.e., physiologic apoptosis. Notably, caspase 14 activation occurs in parallel, and both processes fail to occur in either PAR2 or Casp 14 ko mice. Instead, LB secretion accelerates, while terminal differentiation is delayed in PAR2 ko mice. Since pH-dependent SP activation also releases IL-1α/β from pre-formed pools in the corneocyte cytosol, it is tempting to speculate that either the resultant cytokine cascade and/or pH/SP/PAR2 signaling could provoke pruritus. One or both mechanisms would provide an alternative, 'outside-to-inside', non-neuro-endocrine basis for the initiation of pruritus.

OP19 SPHINGOSYLPHOSPHORYLCHOLINE AND ITCH

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Dryness and impaired barrier function of the skin are clinical signs of patients with atopic dermatitis (AD). The amount of ceramides is markedly reduced in the stratum corneum of AD patients. Changes in the metabolism of ceramides have been thought to be involved in dry skin and impaired barrier function in AD. Although ceramide is synthesized from sphingomyelin by sphingomyelinase, in the stratum corneum of AD, sphingomyelin hydrolysis is mainly due to sphingomyelin deacylase, which converts sphingomyelin to sphingosylphosphorylcholin (SPC) and free fatty acid. Thus, SPC is increased (ceramide is decreased) in the stratum corneum of AD. However, the role of SPC in AD is unclear. In the present study, we investigated the itch-eliciting activities of SPC and related substances and the mechanisms of the SPC action in mice. An intradermal injection of SPC induced scratching as an itch-associated response. Intradermal injections of sphingomyelin and sphingosine were without effects. SPC-induced scratching was suppressed by the mu-opioid receptor antagonist naltrexone but neither by deficiency in mast cells nor the H_1 histamine receptor antagonist terfenadine. The SPC action was inhibited by the 5-lipoxygenase inhibitor zileuton and the leukotriene B_4 (LTB_4) antagonist ONO-4057, but not by the cyclooxygenase inhibitor indomethacin. Administration of SPC to primary cultures of epidermal keratinocytes increased intracellular Ca^{2+} ion concentration and the production of LTB_4, which acts on BLT1 LTB_4 receptors on primary sensory neurons. SPC also increased intracellular Ca^{2+} ion concentration in primary cultures of dorsal root ganglion neurons. These results taken together suggest that SPC is involved in the induction of itch through the actions on primary sensory neurons and epidermal keratinocytes.

CELLULAR BASIS OF ITCH SENSATION *OP20*

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Itch and pain are two distinct sensations. Although our previous study suggested that gastrin-releasing peptide receptor (GRPR) is an itch-specific gene in the spinal cord, a long-standing question of whether there are separate neuronal pathways for itch and pain remains unsettled. Here we selectively ablated lamina I neurons expressing GRPR in the spinal cord of mice. These mice showed profound scratching deficits in response to all of the itching (pruritogenic) stimuli tested, irrespective of their histamine-dependence. In contrast, pain behaviors were unaffected. Our data also suggest that GRPR+ neurons are different from the spinothalamic tract (STT) neurons which have been the focus of the debate. Together, the present study suggests that GRPR+ neurons constitute a long-sought labeled line for itch sensation in the spinal cord.

ITCH SENSITIZATION IN RODENT MODELS *OP21*

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Itch, an unpleasant sensation associated with the desire to scratch, frequently accompanies a variety of skin conditions and systemic diseases. Chronic itch was suggested to involve sensitization of itch-signaling neural pathways. Recent studies suggest overlap between peripheral and central pathways transmitting itch and pain. Sensitization of peripheral and central nociceptive neurons contributes importantly to chronic pain. However, little is known concerning sensitization of pruriceptive neurons. Using ICR mice, repeated application of acetone-ether-water (AEW) to the rostral back induces dry skin associated with significantly increased spontaneous scratching directed to the treatment area. Moreover, pruritogens (5-HT, PAR-2 agonist) injected id within the AEW area elicited significantly greater scratching (hyperknesis) vs. controls, even when spontaneous scratching was subtracted. Hindpaw AEW treatment also increased itch-related biting of the hindpaw. In na・e mice, superficial lumbar spinal neurons with low spontaneous activity responded to pruritogens over a time course consistent with itch. The majority also responded to mechanical and noxious chemical and thermal stimuli, suggesting that itch is signaled partly by a population code. Neurons recorded ipsilateral to an AEW-pretreated hindpaw exhibited significantly greater spontaneous firing and enhanced pruritogen-evoked responses. Scratching significantly inhibited ongoing firing in a manner that was reduced or prevented by spinal application of GABA-A, GABA-B and glycine antagonists. Interestingly, scratch-evoked inhibition was also significantly attenuated (~50%) by cold-block or spinalization at an upper cervical level, indicating supraspinal involvement. Finally, in calcium imaging studies, dorsal root ganglion cells from AEW-treated mice exhibited greater peak responses to 5-HT and the

PAR-2 agonist compared to cells from control mice. These results suggest that chronic itch from dry skin may sensitize peripheral pruriceptive sensory neurons leading, in turn, to central sensitization of superficial dorsal horn neurons. Spontaneous firing of these neurons may trigger itch, and their enhanced excitability may underlie the hyperknesis observed behaviorally.

OP22 ENHANCED SCRATCHING IN A MOUSE MODEL OF CHRONIC DRY SKIN ITCH

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We investigated if spontaneous and acute pruritogen-evoked scratching behavior is enhanced in mice with chronic dry skin itch. We also addressed peripheral sensitization by determining if pruritogen-evoked activity of dorsal root ganglion (DRG) neurons is enhanced in this model. Chronic dry skin on the rostral back of adult ICR mouse was created by twice-daily treatment with acetone and diethyether (1:1) followed by water (AEW). Mice treated with water only (W) served as controls. After 5 treatment days, spontaneous scratching was recorded for 30 min. Then either saline, histamine (35 μg/10 μl), the PAR-2 agonist SLIGRL-NH2 (35 μg/10 μl), or 5-HT (0.03%/ 10 μl) was injected id within the AEW or W treatment area, and animals videotaped another 30 min. Scratching bouts were counted by investigators blinded as to treatment. Cells from cervical DRGs were dissociated and cultured for 18–36 h at 37°C in carbogen. DRG cells were loaded with Fura-2 AM and imaged with a fluorescence microscope to monitor intracellular [Ca++] in response to perfusion of each mediator (all 100 μM). AEW-treated mice exhibited 3-fold greater spontaneous scratching compared to W controls ($p<0.01$). Histamine, SLIGRL-NH2 and 5-HT elicited 2-, 4-and 5-fold more scratching, respectively; in AEW vs. W groups. After subtracting spontaneous scratching, SLIGRL-NH2 and 5-HT, but not histamine, elicited more scratching in AEW vs. W groups ($p<0.001$). DRG cells from AEW-treated mice exhibited a significantly greater peak response to 5-HT, compared to cells from controls. SLIGRL-NH2 excited a higher percentage of DRG cells from AEW- vs. W-treated animals. The increased spontaneous scratching may reflect chronic ongoing itch. The enhanced pruritogen-evoked scratching may represent hyperknesis, i.e. increased itch to a normally itchy stimulus. The calcium imaging data suggest that peripheral sensitization may partly underlie the enhanced scratching elicited by 5-HT and SLIGRL-NH2 in animals with chronic dry skin.

OP23 ETHANOL AGGRAVATES ITCH-RELATED SCRATCHING VIA CENTRAL DEPRESSANT ACTIONS IN HAIRLESS MICE WITH ATOPIC DERMATITIS

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Atopic dermatitis (AD) is a common skin disease accompanied by chronic itching; however, the precise mechanisms underlying this itching remain to be elucidated. We have shown that HR-1 hairless mice fed a special diet, HR-AD, but not a normal diet, develop AD-like skin inflammation with prolonged spontaneous scratching, and that skin barrier dysfunction is involved in the basal scratching. Alcoholic beverages are known to be one of various triggers of itching in patients with AD. Thus, in the present study, the effects of ethanol on scratching in this mouse model were examined, and the underlying mechanisms were pharmacologically analyzed. Eight weeks after the start of HR-AD feeding, oral administration of ethanol (30%, 10 ml/kg) to HR-AD-fed mice caused marked increase in scratching with long duration. By contrast, scratching in normal diet-fed mice was not affected by the oral administration of ethanol. On the other hand, intradermal injection of ethanol did not elicit any scratching response in both mice. The aggravated scratching by oral dosing of ethanol in HR-AD-fed mice (ethanol-induced scratching) was suppressed by either μ-opioid receptor antagonism or local skin anesthesia, as in human itching. Ethanol-induced scratching was relieved by improvement of skin barrier function by an application of petrolatum ointment, while ethanol administration itself did not affect the function. This suggests that ethanol indirectly aggravates the basal scratching. Although antagonism of the transient receptor potential vanilloid-1 did not affect the ethanol-induced scratching, blockade of ethanol actions in the central nervous system (CNS), including γ-aminobutyric acid type A receptor antagonism and *N*-methyl-D-aspartate receptor activation, inhibited it. Taken together, the present study demonstrates that orally administered ethanol markedly aggravates itch-related scratching in HR-AD-fed mice with AD. Furthermore, the CNS depressant actions of ethanol could play a major role in the aggravation.

OP24 ORAL ADMINISTRATION OF DIHOMO-GAMMA-LINOLENIC ACID PREVENTS ITCH IN ATOPIC NC/NGATND MICE THROUGH PGD1 PRODUCTION

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In patients with atopic dermatitis (AD), higher levels of serum linoleic acid (LA) have been reported, whereas those of its metabolites are lower than healthy volunteers. Observations suggest impaired delta-6 desaturase activity and the subsequent altered composition of n-6 polyunsaturated fatty acids (PUFA). Dihomo-gamma-linolenic acid (DGLA) is a biologically effective n-6 PUFA derived from LA and one of important sources of prostaglandins (PG) (particularly 1 series of PGs) as well as arachidonic acid (a source of particularly 2 series of PGs) in vivo. Since PGDs derived from n-6 PUFA have been reported to relieve pruritus in AD, we examined whether oral administration of DGLA prevents development of AD in NC/NgaTnd mice. NC/NgaTnd mice were fed with a DGLA-diet for 8 weeks under in air-uncontrolled conventional circumstances. Clinical skin severity scores were significantly lower in mice fed with DGLA than control mice. Scratching behavior and plasma total IgE levels were also reduced in the DGLA group, in association with histological improvement. DGLA contents in phospholipid s of skin, spleen, and plasma were increased in mice fed with a DGLA-diet. At the end of the experiments, we measured levels of various PGs in each tissue and found that PGD1 levels were markedly increased in mice fed with a DGLA-diet than control

mice. Reduction in severity of dermatitis and scratching behavior correlated closely with the increase of PGD1 levels. On the other hand, the increase in levels of PGE2; in control mice was associated with severity of dermatitis. These findings indicate that oral supplementation of DGLA prevented itch in NC/NgaTnd mice through PGD1 production resulting in suppression in severity of dermatitis. DGLA in phospholipids may be a compound of key importance in regulation and prevention of AD.

OP25 FLAKY TAIL MOUSE AS A POSSIBLE MODEL OF ATOPIC DERMATITIS: PRURITUS-ASSOCIATED RESPONSE INDUCED IN FLAKY TAIL MOUSE

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Background: Atopic dermatitis (AD) is a chronic, inflammatory disease of the skin, characterized by intense pruritus and skin barrier defect. The barrier abnormality, a loss-of-function mutation in the gene encoding filaggrin (*FLG*) which is linked to the incidence of AD, is a recently-discovered but important factor in the pathogenesis of AD. In further explorations of the influence of *FLG* mutation on AD, flaky tail (*ft/ft*) mice, in which filaggrin is essentially not detected, might be useful. In this study, we sought to establish a new mouse model to evaluate the pruritus as clinical impact of barrier dysfunction from the perspective of AD using *ft/ft* mice. **Methods:** Mice were raised under specific-pathogen-free (SPF) conditions, and clinical manifestations, histology of the skin, integrity of the skin barrier, and total serum IgE levels were measured. In addition, mite extract (*Dermatophagoides pteronyssinus*)-induced dermatitis models was used to predict sequential event. Scratching behavior was measured in detail using the Sclaba Real system. **Results:** Even under SPF conditions, the majority of *ft/ft* mice developed clinical and histological eczematous skin lesions with elevated pruritus, number of mast cells, and skin barrier defect. The *ft/ft* mice started to scratch at the age of 10 weeks, although erythema and scaling of the skin occurred at the age of 10 weeks. In addition, *Dermatophagoides pteronyssinus* extract-induced dermatitis was enhanced in *ft/ft* mice accompanied by spontaneous intense scratching behavior. **Conclusion:** These results suggest that the *ft/ft* mice are proposed as an animal model of AD, and provide several lines of evidence suggesting that the skin barrier defect plays a key role in the pathogenesis of AD and enhancement of pruritus.

OP26 PRIMARY AFFERENTS AND THE SENSATION OF ITCH

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The neuronal pathways for itch have been characterized mainly using histamine, but chronic itch can be resistant to anti-histamine treatment. We sought to investigate the peripheral neural mechanisms of histamine-independent itch. Since spicules from the plant *Mucuna pruriens* (cowhage) have been anecdotally reported to produce itch without flare, we performed psychophysical experiments to compare the mechanisms underlying cowhage- and histamine-induced itch. While both produced itch of similar magnitude, cowhage- and histamine induced itch were not correlated; some subjects had intense itch to cowhage and little itch to histamine, and visa versa. Histamine, but not cowhage, led to a large area of vasodilation. Pretreatment with a topical antihistamine blocked histamine- but not cowhage-induced itch. Capsaicin desensitization of the skin abolished cowhage itch without significantly altering histamine itch. Therefore, cowhage produces itch through a population of capsaicin-sensitive nerve fibers distinct from afferents mediating histamine itch. In electrophysiological studies in anesthetized monkey the responsiveness of single myelinated and unmyelinated afferents to application of cowhage spicules or intradermal injection of histamine and capsaicin was investigated. The majority of mechano-heat sensitive C-fibers (CMHs) responded prolonged to cowhage or histamine, but not to capsaicin. The average response to cowhage was more than twice the histamine response, and responses were not correlated. The cowhage response was characterized by action potential bursts. A subset of CMHs with a quickly adapting response to a stepped heat stimulus gave the biggest cowhage response. Cowhage did not activate mechanically-insensitive C-fibers, but a subset responded vigorously to histamine. Some mechanically sensitive myelinated nociceptors (A-MSAs) responded vigorously to cowhage. A different subset of A-MSAs responded weakly to histamine. Mechanically-insensitive myelinated nociceptors (A-MIAs) were unresponsive to cowhage; but a few responded to histamine. These results suggest that different subpopulations of A and C fiber nociceptors may mediate cowhage- and histamine-induced itch sensation.

OP27 STUDIES OF PRURICEPTIVE AND NOCICEPTIVE RESPONSES OF SPINOTHALAMIC TRACT (STT) NEURONS IN MONKEYS

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The STT in primates has long been thought to play an important role in itch. However, few studies have characterized the responses of such cells to itch-producing stimuli. We have used single cell recording methods to identify and characterized STT neurons in monkeys. We have found that about one-quarter of STT neurons respond to pruriceptive stimuli. Intradermal injections of histamine and application of cowhage, which produces a form of itch that is not dependent on histamine, activate almost completely separate populations of STT neurons. All pruriceptive STT were also activated by noxious stimuli, suggesting that information related to itch is transmitted by polysensory neurons. No evidence was found for the existence of primate STT neurons that were activated exclusively by pruriceptive stimuli. Stroking of the skin with a cotton swab was found to produce greater responses following responses to itch-producing stimuli. This suggests that the hyperknesis produced by stroking of the skin is the result of the increased responses of STT neurons. We also found that scratching activates STT neurons during their resting state or after injections of capsaicin but inhibits STT neurons during responses to histamine, suggesting that the inhibitory effects of scratching are dependent on a

state-dependent form of inhibition. We are currently attempting to determine whether such inhibition is dependent upon descending contributions from the brain or is entirely segmental.

OP28 SIMILAR MECHANISMS OF SENSITIZATION IN ITCH AND PAIN?

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Mediators that specifically cause acute and chronic itch are searched for since decades. After a specific neuronal pathway for histamine-induced itch had been discovered one might have expected that other mediators responsible for the histamine-independent itch would be uncovered. However, recent data show astonishingly similar mediators and mechanisms of neuronal sensitization in the periphery and the central nervous system in itch and pain, such as nerve growth factor (NGF), proteinase-activated receptors (PAR-2) and endothelin on the peripheral level and identical patterns of sensitization on spinal level. Even more confusing, capsaicin which provokes strong pain in human subjects can also elicit itch when applied into the epidermis on a minute spicule. Thus, obviously not only activation of specialized "itch fibers", but also certain activation patterns of fibers normally involved in the pain pathway can elicit itch. Given that there is an overlap in mechanisms for chronic pain and itch it is of major importance to exchange information and results between itch and pain researchers: Currently pain researchers try to find molecular mechanisms for neuropathic pain in a patient oriented fashion linking clinical data to functional assessments and histology. Both sensory (such as TRPV1 or TRPA1) and axonal channels (such as NaV1.7 or NaV1.8) have been hypothesized as the source of ongoing activity leading to pain. It appears mandatory to expand the same approach to patients suffering from chronic pruritus.

OP29 NEUROPHYSIOLOGICAL AND PSYCHOPHYSICAL STUDIES ON HISTAMINERGIC AND NON-HISTAMINERGIC ITCH

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In microneurography experiments we have shown that the pruritus induced by cowhage (*mucuna pruriens*) and by histamine is mediated by different peripheral pathways. Cowhage excited all tested mechano-sensitive C-fibers (CMH, polymodal nociceptors) to different degrees, while histamine activated a subgroup of the mechano-insensitive C-fibers (CMi, "sleeping" nociceptors). Histamine-sensitive CMi units are not exclusively sensitive to this agent, however, they respond also to other endogeneous mediators, e.g. prostaglandine E_2. Most of them are also capsaicin sensitive. These findings prompted us to explore the sensory qualities of different itch stimuli in double blind experiments comparing native cowhage spicules with inactive spicules coated with histamine or capsaicin, similar to a procedure introduced by LaMotte and coworkers (Pain 144, 2009). 10–15 spicules were inserted to the lower forearms of subjects on an area of approximately 12 mm^2. The itch and pain-related sensations were rated on 24 scales labelled by sensory adjectives from an itch questionnaire. The rating on the "itching" scale was highest for histamine. The capsaicin stimulus led to a rating on the "itching" scale comparable to that of cowhage, but it brought about higher ratings on the scales "pins and needles", "prickeling", "sharp", "biting" and "painful", all depicting pain qualities. When the three stimuli were rated alternatingly on scales for "burning" and "itching" over periods of 7 min, "burning" was prominent during the first minute after spicule application irrespective of the stimulus. When capsaicin was applied, however, "burning" sensations were dominant for more than two minutes while the itching component became more marked afterwards. The implications of these findings for the encoding of itching and painful sensations will be discussed.

NEUROPATHIC ITCH: INSIGHTS FROM PATIENTS AND RAT MODELS OP30

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Neuropathic itch is caused by neurological dysfunctions that produce hallucinations of pruritogenic stimuli, when there are none. Neuropathic itch triggers the same reflex and volitional scratching as normal itch, even though scratching provides only fleeting relief. Some patients scratching even causes self-injury, a poorly understood phenomenon often misattributed to psychopathology. The relationship of neuropathic itch to normal itch mechanisms and to neuropathic pain remains unclear. Postherpetic itch (PHI) after zoster is one of the best-studied neuropathic itch conditions. Study of one patient suggested that self-injurious scratching requires profound cutaneous de-afferentation, which allows painless scratching. Preliminary epidemiological study of PHI identified it in 1/3 to 1/2 of shingles patients; it was independent of sex and age. In contrast, PHI is most common after shingles of the head and neck, hinting at different susceptibility to neuropathic itch in different body areas. Neuropathic itch can also develop after central (brain or spinal-cord).injuries and MRI localization is helping to identify central itch pathways. Cavernous hemangiomas have been particularly implicated. Pathological features including gliosis and hemosiderin efficiently trigger ectopic firing. A similar rat spinal-cord-injury model provides additional insights. Dorsal-horn injections of quisqualic acid, a neurotoxin, cause some rats to compulsively scratch the affected dermatome. Scratching develops only if there is deep-dorsal-horn necrosis plus superficial-lamina preservation. NK-1 receptive neurons are also implicated. Because self-injurious scratching is difficult to explain by central mechanisms alone, we evaluated whether the injections damage peripheral axons as well as dorsal-horn cells. Measuring skin innervation in injected rats that did or did not scratch showed that intramedullary quisqualate profoundly damages small-diameter peripheral afferents, and rats that overgroom have the worst peripheral degeneration. Thus, some forms of central itch may also involve cutaneous de-afferentation.

PSYCHOPHYSICAL STUDIES OF ITCH IN HUMANS: IMPLICATIONS FOR NEURAL CODING OP31

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Psychophysical studies of chemically evoked itch, nociceptive sensations and dysesthetic cutaneous states are useful in

identifying the neural coding mechanisms of itch. They help to define the sensory phenomena that must be accounted for in the responses of candidate pruriceptive neurons. In psychophysical studies in humans, a minute amount of histamine, capsaicin, or a cysteine protease, delivered to a punctate region of skin by means of a single, chemically inert, cowhage spicule, evokes a sensation of itch typically accompanied by nociceptive sensations of pricking/stinging and burning. Dysesthesias sometimes develop in the skin surrounding the application site. These can include itch to stroking (alloknesis) and/or enhanced pain or itch to pricking the skin (hyperalgesia or hyperknesis, respectively). When increasingly larger amounts of chemical are injected into the skin via needle and syringe, the qualities of sensation and dysesthesias are the same for histamine, though increased in likelihood and magnitude. But for capsaicin, nociceptive sensations and allodynia (to stroking) are evoked and enhanced in the place of itch and alloknesis. A heuristic, neuronal model is devised to integrate these observations with the results of electrophysiological recordings obtained from pruriceptive and nociceptive-specific sensory neurons in mouse, monkey or human.

OP32 THE NEW APPROACH TO STUDYING NEUROPHYSIOLOGICAL MECHANISMS OF ITCH: EVOKED POTENTIALS TO ELECTRICAL AND THERMAL STIMULATION IN PATIENTS WITH ATOPIC DERMATITIS

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Objective: Itch is defined as a subjective sensation that provokes a desire to scratch. Its mechanisms are not fully understood, though it is closely related to pain and is known to be conducted along thin unmyelinated fibers. Aim of our research was to study central mechanisms of itch by obtaining brain answers to electrical and innovative selective thermal stimulation in patients with atopic dermatitis (AD). **Materials and Methods:** Somatosensory evoked potentials (SSEP) were registered in 17 patients with very severe (SCORAD 77±5, itch 9±1) and 24 patients with severe (SCORAD 53±13, itch 7±1) AD. Long-latency evoked potentials (LLEP) were registered by means of Contact-Heat Evoked Potential Stimulator (CHEPS) in 24 AD-patients (SCORAD 53±13, itch 7±1) and 24 healthy volunteers. **Results:** Group of patients with high severity of AD and itch showed increase of both early and late EP and makeable decrease of sensory and algetic thresholds, in the group of patients with less severe degree of AD and itch similar changes were observed but only to intensive painful stimulation. Thus 2 groups demonstrated brain hyperactivity, which correlated with the severity of AD. Thermal EP were obtained in AD patients in form of negative-positive complex as well as in control group however larger variations of amplitudes and latencies were observed. When compared with control group significant latency prolongation of LLEP to cheek stimulation in AD patients ($p<0.01$) and to forearm stimulation ($p<0.05$) were revealed. **Conclusion:**Acquired data demonstrate central sensitization and disturbances of thin fibers afferentation in AD patients. We hypothesize that AD patients have initial thin fibers insufficiency which can facilitate itch initialization and chronification. New data enlarge our knowledge of pathogenesis of atopic dermatitis, proves psychotropic therapy administration with the purpose of central sensitization lowering and contributes to developing new methods of treatment.

MECHANICALLY EVOKED ITCH IN HUMANS *OP33*

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Background: Several reports recently published suggest the presence of more than one neural pathways for itch. The specificity of nerves for histamine-induced itch has been supported by their mechano-insensitivity. On the other hand, cowhage-responsive nerves were recently reported to be mechano-sensitive. However, there is a suspicion that cowhage-responsive nerves reported might represent the ones for pain, not for itch, because cowhage induces mixed sensations of itch and pain. **Objective**: To clarify the presense of mechano-sensitive nerves for itch by developing a reproducible method to evoke itch mechanically. **Method**: The device by which the intensity and frequency of vibrating stimuli could be controled was developed. A ring shaped probe connected to this device was put onto the skin of healthy human volunteers and stimuli were started. **Result**: Pure and intense itch was reproducibly evoked. **Conclusion**: This study clearly demonstrates the presence of mechano-sensitive nerves conducting itch.

SELF-HYPNOSIS TRAINING FOR SYMPTOM MANAGEMENT: APPLICATIONS FOR PAIN AND ITCH *OP34*

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Evidence from controlled trials support the efficacy of self-hypnosis training for chronic pain management. Research has also shown that activity in many of the central nervous system structures associated with pain is influenced by hypnotic analgesia. These structures include the primary and secondary sensory cortices, the anterior cingulate cortex, the prefrontal cortex, and insular cortex. The experience of itch is associated with many of the nervous system structures that also process pain information. This suggests the possibility that patients with chronic itch might benefit from learning self-hypnosis strategies for itch management. A number of published case studies reporting benefits of hypnosis for reducing itch are consistent with this hypothesis. These findings support the development of hypnosis protocols for itch management, and research to test the efficacy of these protocols in patients suffering from chronic itch.

INHIBITION OF MOUSE SCRATCHING BEHAVIOR BY TACROLIMUS AND ITS MECHANISMS *OP35*

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Itching is the most important problem in many allergic and inflammatory skin diseases especially in atopic dermatitis. We established allergic dermatitis models in mice by painting a hapten repeatedly and evaluated the effects of tacrolimus and dexamethasone in ethanol solutions on the allergic inflammation and scratching behavior comparatively. Repeated hapten application caused a potent dermatitis with increased serum IgE levels and elevated expression of Th2 cytokine mRNAs. At the same time, frequent scratching

behavior was induced after the hapten application. Although topical application of dexamethasone potently inhibited the dermatitis, it failed to affect the scratching behavior. In contrast, tacrolimus given topically apparently inhibited the scratching behavior, although its anti-inflammatory effects were weaker than those of dexamethasone. Tacrolimus inhibited nerve fiber extension and nerve growth factor expression, and reduced substance P content in the skin. Furthermore, tacrolimus increased semaphorin 3A expression in the epidermis. Dexamethasone did not show such effects. These results indicate that scratching behavior observed after hapten application does not seem to be a result from inflammation caused by the hapten and that tacrolimus inhibits the scratching behavior through mechanisms distinct from anti-inflammatory mechanisms shown by dexamethasone. Inhibition of nerve fiber extension, inhibition of nerve growth factor expression, decrease in skin substance P content, and increase in semaphoring 3A expression may contribute to the inhibition of scratching behavior by tacrolimus in mice at least in part.

OP36 TRANSIENT RECEPTOR POTENTIAL VANILLOID 3 (TRPV3) HAS A ROLE IN THE DEVELOPMENT OF ITCHY DERMATITIS

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In 1976, DS-*Nh* mice were bred from a colony of the DS inbred strain with a hairless phenotype and an autosomal dominant inheriting mode. Positional cloning analysis has revealed that the cause of hairlessness in DS-*Nh* mice is a Gly573Ser substitution in the transient receptor potential vanilloid 3 (TRPV3). This is a non-selective cation channel activated by warmth and is highly expressed in basal keratinocytes in the skin. DS-*Nh* mice develop spontaneous dermatitis and are considered a good model of human atopic dermatitis; partly because their scratching behavior becomes significantly more severe as the disease progresses. We recently showed that these phenotypes are not segregated during the sequential crossing procedure and thus speculated that TRPV3^{Gly573Ser} could also cause itchy dermatitis in DS-*Nh* mice. To elucidate the involvement of TRPV3 in the development of a certain type of dermatitis, TRPV3^{Gly573Ser} transgenic mice with the transgene including the putative promoter sequence in the 5' region of the TRPV3 gene were pathologically and serologically investigated. Our data revealed that transgenic mice spontaneously developed allergic and pruritic dermatitis in addition to their hairless phenotype. Wild-type mice did not display these phenotypes when maintained under the same conditions. We raised C57BL/6-*Nh* congenic mice using general breeding methods to investigate the penetrance of the TRPV3^{Gly573Ser} gene in respect of dermatitis. Interestingly, these mice developed spontaneous scratching behavior separately from dermatitis. We proposed that TRPV3^{Gly573Ser} is a cause of pruritus and/or dermatitis associated with scratching. We also suggested that TRPV3 represents a therapeutic target for pruritus and itchy dermatitis.

OP37 ROLE OF PROTEINASE-ACTIVATED RECEPTORS AND PEPTIDASES IN SKIN INFLAMMATION AND PRURITUS

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Endogenous serine proteinases such as thrombin, mast cell tryptase, various trypsins or cathepsin G, for example, as well as exogenous proteinases (bacteria, fungi, house dust mite) are highly active mediators implicated in tissue homeostasis and disease. Moreover, keratinocytes and immune cells abundantly generate kallikreins (KLK) which play an important role in epidermal homeostasis and inflammation. The role of endogenous serine proteases in pruritus, however, is still unclear. The biological capacities of proteinases in tissues and cells suggest important roles during inflammation and immune response. Certain of these effects can be attributed to the activation of a new subfamily of G protein-coupled receptors, defined as proteinase-activated receptors (PARs). Understanding the underlying mechanisms regulating PARs and the effects induced by those receptors through proteinases may lead to novel strategies for the treatment of inflammatory skin diseases and pruritus. In the skin, PARs are widely expressed by cells involved in immune responses and inflammation (keratinocytes, endothelium, leukocytes, nerves), regulate endothelial-leukocyte interactions, modulate the secretion of inflammatory mediators, and control the function of sensory nerves with respect to neurogenic inflammation, pruritus and pain. In itch, proteases appear to represent an alternative pathway to histamine-induced itch since activation of certain PARs induce histamine-independent pruritus. Thus, suppressing proteinase and/or PAR-inuced pruritus may be a novel option for the treatment of pruritus and pruritic diseases with or without an inflammatory component. This talk also gives an overview about novel mechanisms how protease- and peptidase receptor internalization and resensitization is orchestrated to prevent overstimulation and thereby disease.

TRP CHANNEL FUNCTIONS IN THE SKIN KERATINOCYTES *OP38*

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Transient receptor potential V3 (TRPV3) and TRPV4 are heat-activated cation channels expressed in keratinocytes. It has been proposed that heat-activation of TRPV3 and/or TRPV4 in the skin may release diffusible molecules which would then activate termini of neighboring dorsal root ganglion (DRG) neurons. We found that ATP is such a candidate molecule released from keratinocytes upon heating in the co-culture systems. We found that increase in cytosolic Ca2+-concentration in DRG neurons upon heating was observed only when neurons were co-cultured with keratinocytes, and this increase was blocked by P2 purinoreceptor antagonists, PPADS and suramin. In a co-culture of keratinocytes with HEK293 cells (expressing P2X2 as a bio-sensor), we observed that heat-activated keratinocytes secretes ATP, and that ATP release is compromised in keratinocytes from TRPV3 deficient mice. Thus, we concluded that ATP is a messenger molecule for mainly TRPV3-mediated thermotransduction in skin. Then, we asked what TRPV4 is doing in the skin keratinocytes. Dehydration of the skin is prevented by epidermal barriers formed by tight-junctions and adherens-junctions among differentiated keratinocytes. Maturation of the junctions occurs through actin organization and cell stratification during

Ca^{2+}-dependent keratinocyte differentiation. We hypothesized that Ca^{2+}-permeable TRPV4 channels play a key role in barrier formation because these channels are activated by physiological skin temperature, thereby increasing intracellular Ca^{2+} which is important for keratinocyte differentiation. We found that Ca^{2+} influx via TRPV4 is involved in the maturation of cell-cell junctions via binding to β-catenin and E-cadherin. TRPV4-deficient mice displayed impairment of cell-cell junction-dependent skin barrier function. TRPV4-deficiency caused immature actin organization, immature stratification and abnormal junctional structures in keratinocytes, resulting in impaired barrier function in vitro. Cytosolic Ca^{2+} increase at 33°C and following Rho activation were significantly lower in TRPV4-deficient keratinocytes. These results support this novel and specific role for TRPV4 in skin keratinocytes.

OP39 IL-31: AN IMPORTANT PLAYER IN THE SCENE OF ITCH

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Background: IL-31, a recently discovered cytokine, has been shown to be involved in atopic dermatitis and pruritus. The expression of the functional receptor subunits for IL-31, IL-31RA and OSMRβ, in murine dorsal root ganglia (DRG) neurons and the dorsal horn of the spinal cord suggest that IL-31 may play a specific and centrally-mediated role for itch, and possibly for pain. **Methods**: We investigated the role of IL-31 in itch and itch sensitization. In a model of oxazolone-induced chronic atopic dermatitis (application for 3 weeks), IL-31 was injected into the nape neck skin of wild-type (WT) and IL-31 receptor deficient (IL-31RA KO) mice. The impact of IL-31 on itch was assessed by analysis of scratch events. The effect of IL-31 on Ca^{2++} release and interaction with the TRPV1 ion channel was investigated *in vitro*. **Results**: Scratching bouts were more prominent in WT than in IL-31RA KO mice after single subcutaneous IL-31 injections. The pruritogenic effect of IL-31 was significantly enhanced after topical oxazolone treatment in WT mice. Without IL-31 injection, oxazolone-sensitized IL-31RA KO mice scratched significantly more frequently than WT mice. Treatment of cultured murine DRG neurons with IL-31 at pH 5.8 clearly demonstrated that IL-31 directly activates sensory neurons and communicates with TRPV1. **Conclusion**: Thus, ligation of IL-31R by IL-31 activates and sensitizes sensory neurons to transmit itch. We show that IL-31 sensitizes the TRPV1 ion channel and likely modulates other neuronal receptors. IL-31 may be involved in cross-talk with other receptors and thereby may contribute to pruritus and neurogenic inflammation.

OP40 ARTEMIN IS EXPRESSED IN SUBSTANCE P-TREATED DERMAL FIBROBLASTS, AND CONTRIBUTE TO THE PERIPHERAL NERVE FIBER SPROUTING

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Substance P (SP) has demonstrated various functions such as chemical mediator in the case of immunoresponse, and neurotransmitter in subjective symptoms like pain and itch. Although dermal fibroblasts may be candidate SP-responsive cells, little is known about the effect of SP. We have investigated the expression profiling of genes that are induced by substance P-treatment in normal human dermal fibroblast (NHDF) using macro-gene array. Based on this study, we focused on de novo artemin (ARTN), which is a member of the glial cell line-derived neurotrophic factor related family, gene transcription in NHDF after substance P-stimulation. SP-treated NHDF-derived conditioned medium induced a proliferative response in a neuroblastoma cell line, and this phenomenon was suppressed by neutralization of ARTN. Furthermore, we verified that dermis of atopic dermatitis (AD) skin lesions exhibit intense immunoreactivity for ARTN. In situ hybridization assay also revealed that expression of ARTN mRNA in dermal fibroblast was observed in AD skin lesion, but not in healthy control. Colabeling with artemin and its potent receptor GFRα3 showed massive sprouting of GFRα3-positive peripheral nerve fibers in ARTN accumulated dermal areas. This finding raised the hypothesis that artemin might contribute to peripheral nerve sprouting. To support of this assumption, SP-induced elongation of peripheral nerve fiber into epidermis was not observed in GFRα3 knockout mice. These results indicate the novel functional aspects of substance P, and may lead to a better understanding of novel mechanisms of altered skin innervation in atopic dermatitis.

TOPICAL CHOLECYTOKININ DEPRESSES ITCH-ASSOCIATED SCRATCHING BEHAVIOR IN MICE *OP41*

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Cholecystokinin (CCK) is known as a neuropeptide in central nervous system (CNS) as well as a peptide hormone in gastrointestinal tract. CCK is the most abundantly present neuropeptide in CNS and is involved in numerous physiological functions such as anxiety, depression, psychosis, learning/memory processes, and feeding behavior. Furthermore, CCK has anti-opioid properties, exerts a nociceptive effect in spinal cord, and also exists in peripheral nervous system. By a message array system, we found that the expression of CCK receptor (CCK2R) was enhanced in epidermal keratinocytes (KC) cultured with substance P (SP), a pruritogenic neuropeptide. This urged us to investigate the role of CCK on the peripheral pruritus. To initially investigate the effects of CCK on the itch-associated response, ICR mice were painted with various CCK on the skin and administered intradermally with SP, and the frequency of scratch toward the injected site by hind paws was counted for the first 20 min. The scratch was significantly reduced in incidence by topical application of sulfated-CCK8 (CCK8S), non-sulfated CCK8, or CCK7S before SP injection, but not affected by CCK7 or CCK6. By real-time PCR analysis, mRNA for CCK2R was expressed in KC, fetal-skin derived mast cell

(FSMC) and rat pheochromocytoma cell line (PC12). We added CCK to the cultures of FSMC and PC12, and detected an elevation of intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) by confocal recording. The addition of CCK to Fluo-4, AM-loaded FSMC induced a transient elevation of $[Ca^{2+}]_i$ in FSMC but not in PC12. These *in vivo* and *in vitro* findings suggest that topical CCK exerts an anti-pruritic effect, and mast cells may be at least one of the targets of CCK. CCK might be clinically useful as topical reagent because of this novel potency.

OP42 THE ROLE OF SKIN OPIOID RECEPTOR SYSTEM IN ITCH

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Opioid receptors are key players in induction of chronic itch. This could be confirmed using opiate receptor knockout mice experiments and clinical studies on patients with chronic itch. We have induced a dry skin dermatitis as a model for chronic itching on μ-(MOR) and κ-(KOR) opioid receptor knockout (KO) mice. MOR KO mice scratched significantly less than wild type (WT). Additionally the epidermal hypertrophy caused by chronic dermatitis and the amount of epidermal nerve endings in MOR KO mice were significantly decreased than in WT mice. KOR KO mice showed similar scratching behavior as MOR KO mice; however the changes were less significant. In addition, we performed a double blind, placebo controlled, cross over study using topically applied opioid receptor antagonist, Naltrexone, on patients with pruritus in atopic dermatitis. The results revealed significant effects of the topical application of Naltrexone in patients with chronic pruritus (45% improvement of pruritus by VAS compared to placebo, n=24), but not in patients with acute pruritus (7%, n=15). These studies establish the clinical relevance of MOR system and the peripheral, epidermal nerve endings in chronic pruritus and warrant further research and therapeutic potential for such research.

OP43 DIFFERENTIAL MODULATIONS OF ITCH SCRATCHING BY ENDOGENOUS OPIOID PEPTIDES IN THE MONKEY SPINAL CORD

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Itch (pruritus) is a significant clinical problem that afflicts a large number of humans and it is treated by a variety of pharmacological agents with variable success. However, little effort has been devoted to understand the receptor mechanisms by which itch is elicited, leaving a large deficiency in the basic research of pruritus. Humans and monkeys have similar thresholds for detecting stimuli and the neural systems responsible for sensations in both species may be fundamentally similar. Therefore, it is useful and important to conduct studies using monkeys to elucidate the receptor mechanisms underlying pruritus and potential antipruritic drugs. Early studies have shown that intrathecal administration of morphine dose-dependently produces both itch/scratching and antinociception in monkeys and this observation parallels closely with the behavioral effects of spinal morphine in humans. More importantly, recent primate studies have demonstrated that activation of central mu opioid receptor (MOR), not other opioid receptor subtypes, elicits profound and long-lasting scratching responses. Non-sedative and non-antinociceptive doses of kappa opioid receptor (KOR) agonists can attenuate MOR agonist-induced scratching without interfering with antinociception. Using pharmacological approaches, the aim of the study was to determine the involvement of endogenous opioid peptides with different binding affinities in itch scratching responses in monkeys. Among various endogenous opioid peptides including endorphins, dynorphins, and enkephalins tested, intrathecal administration of a MOR-preferring ligand, beta-endorphin (10–100 nmol), dose-dependently elicited profound scratching responses. In contrast, intrathecal administration of enkephalins only elicited mild scratching. More interestingly, intrathecal administration of a KOR-preferring ligand, dynorphin-A (100 nmol), was able to attenuate beta-endorphin-induced scratching when dynorphin-A was combined with beta-endorphin as a mixture. These findings suggest that itch can be differentially modulated by MOR versus KOR in the spinal cord of primates and it may have a broader implication in patients with various skin diseases *endogenously*.

BRAIN OPIOID RECEPTOR RESPONSES TO PSYCHOLOGICAL STRESS IN ATOPIC DERMATITIS MODEL MICE *OP44*

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Objectives: Atopic dermatitis is a common pruritic inflammatory skin disease. It has been well recognized that environmental factors such as mites and dusts and psychological stress exacerbate atopic dermatitis. Recently, we have demonstrated that psychological stress by itself can induce scratching behaviour and trigger atopic dermatitis-like skin changes in atopic dermatitis model mice, NC/Nga. Additionally, we have shown that the pretreatment with corticotropin-releasing factor (CRF) inhibits scratching behaviour induced by psychological stress. In this study, to explore the mechanism how psychological stress can induce itch and also how CRF inhibits scratching behaviour induced by psychological stress, we investigated the expression level of opioid receptors (μ and κ) mRNA in brain as well as other parameters. **Results:** Under SPF condition, psychological stress elicited atopic dermatitis-like skin lesions along with the increased level of serum IgE in NC/Nga mice. Both μ-opioid receptor antagonist and CRF suppressed scratching behaviour. Psychological stress decreased the mRNA expression of κ-opioid receptors in brain, and pretreatment with CRF restored the mRNA levels of κ-opioid receptors to those of control mice. On the other hand, psychological stress increased the mRNA expression of μ-opioid receptors in brain, and pretreatment with CRF restored the mRNA levels of μ-opioid receptors to those of control mice. **Conclusion:** Our data indicate that CRF may suppress stress-induced scratching behaviour via through the restoration of altered expression of μ and κ-opioid receptors in brain.

OP45 IMPLICATIONS FOR PERIPHERAL OPIOID SYSTEMS TO PRURITUS

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The mu- and kappa-opioid systems play pivotal roles in the modulation of pruritus in the central nervous system. Opioid-induced pruritus is a well-known side effect in pain treatment with morphine and other mu-opioid receptor (MOR) agonists in humans. In contrast, MOR antagonists (e.g. naloxone and naltrexone) and kappa-opioid receptor (KOR) agonists (e.g. nalfurafine) are known to suppress pruritus in patients with chronic renal failure, cholestasis and atopic dermatitis. It is therefore reasonable to conclude that the mu-opioid system is itch-inducible, whereas the kappa-opioid system is itch-suppressive at the central level. Recent studies have also suggested a possible role of peripheral opioid systems in pruritus. One study has demonstrated that topical application of MOR antagonists in the skin inhibited pruritus in patients with atopic dermatitis. Another study has indicated that chloroquine-induced scratching in mice was antagonized by a peripherally restricted KOR agonist. This imply that MOR antagonists or KOR agonists have antipruritic effects at the peripheral level. Moreover, our recent study showed that the kappa-opioid system was downregulated in the epidermis of patients with atopic dermatitis, but the mu-opioid system showed normal levels. The downregulation of the mu-opioid system and the restoration of the kappa-opioid system by psoralen-ultraviolet A therapy were found in patients with atopic dermatitis, concomitant with a decrease of pruritis. These suggest that epidermal opioid systems are associated with the modulation of pruritus in atopic dermatitis. Sensory neurons also expressed MOR and/or KOR. More recently, we reported that some MOR+ fibers expressed gastrin-releasing peptide, an itch-specific mediator, in mouse skin with atopic dermatitis. Thus, this raise the possibility that the opioid receptors on peripheral nerve fibers are directly linked to the modulation of itch. Altogether, these findings may help us to understand the control mechanism of itch at the peripheral level.

OP46 UPDATE ON NC/NGATND MICE AS AN ATOPIC DERMATITIS MODEL

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The hypersensitivity and barrier dysfunction of the atopic skin play a pivotal role in the exacerbation of atopic dermatitis (AD) conditions. Itch is one of the most serious clinical symptoms of AD, which is induced by local extension of sensory nerve fibers, neurogenic inflammation, and release of chemical mediators from mast cells. Epidermal hyperplasia is one of the typical pathological manifestations of AD, and proliferating keratinocytes produce various cytokines including NGF. NGF is capable of promoting the extension of sensory nerve fibers in the dermis; thereby probably triggering a vicious itch-scratch cycle. Although complicated immunological disturbances have been proposed, the exact pathogenesis of AD is not completely understood. NC/NgaTnd mice spontaneously develop AD-like skin lesions that are pathologically and immunologically quite similar to those found in human AD; therefore, this inbred strain is an appropriate animal model for the screening of novel therapeutic agents for the treatment of AD. Recently, we generated a novel NF-κB inhibitor, IMD-0354, and evaluated its efficacy as a therapeutic agent for some disorders related to NF-κB activation. To investigate the possible involvement of NF-κB in the development of AD, 1% IMD-0354 ointment was applied daily to NC/NgaTnd mice with severe dermatitis. During 2 weeks of treatment, scratching behavior decreased and severity of dermatitis reduced in mice treated with IMD-0354. Based on histological examinations, the hyperplasia of keratinocytes and their NGF production significantly reduced in IMD-0354-treated mice. Furthermore, IMD-0354 suppressed the neurite outgrowth of NGF-stimulated pheochromocytoma cells, IgE production from B cells, and IgE-mediated activation of mast cells in vitro. These findings suggest that NF-κB is a good target to control itch in AD. Since we have recently succeeded in generating mast cell-deficient NC/NgaTnd-KitW-sh mice, the possible involvement of mast cells in itch/scratch triggering will be discussed in this session.

INTRACTABLE ITCH IN TERMINAL CARE OP47

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Intractable itch in terminal diseases is rare. No more than a few cases a year are seen in large specialised centres. Clinical trials are difficult if not impossible. Most of the itch seen in this context can be classified as itch of cholestasis. Although cholestasis can be relieved in the early stages by bile duct cannulation, it can be difficult or even impossible to do this in terminal care. In addition, relief of bile duct obstruction may not relieve all itching. It is thought that cholestasis itch can be relieved by opioid antagonists such as naloxone or naltrexone. However, in the context of terminal care this usually means exchanging itching for pain. Buprenorphine looks to be a better choice, as this drug not only has the potential to block access of the endogenous opioids to the opioid receptors but also, at the same time, has a potent analgesic effect. Alternatively, selective serotonin reuptake inhibitors (SSRIs) have been used successfully in this context and three controlled trials have assessed the use of SSRIs. SSRIs also appear to be effective in paraneoplastic itch. This itch is defined as an itch that accompanies or precedes a diagnosis of malignant disease, decreasing or disappearing when the disease is successfully controlled but the reappearance of which may herald a recurrence of the tumour. Paraneoplastic itch can be manifested as dermatosis but may also appear with no skin abnormalities. In the case of dermatosis, topical treatment may be of great value. It seems that the paraneoplastic itch accompanying lymphoma is a different entity and does not respond well to treatment with SSRIs, although data are scarce. As in other types of systemic itch, antihistamines appear to have limited or no value in its treatment.

NEUROPEPTIDERGIC INTRACTABLE ITCH: PROBLEMS AND SOLUTIONS OP48

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Itch can be considered in limited but relevant cases an intractable disorder i.e. not responding to well established and traditio-

nal or innovative treatments. The role of neuropeptides (NPs), neuromediators and neurohormones is under investigation in this type of itch which could be defined in specific cases as "neuropeptidegic itch". Neuropeptidergic Acral Dysesthesia,in fact, is a typical example of neuropeptidergic itch in its localized form. Neurophysiological mechanisms presently described in itch-specific and non specific neural pathways are mostly NP-dependent as well as the main biologic activities of the cerebral itch-related areas. The role of NPs in itch-related neurogenic inflammation and in neural sensitization is presently under investigation and is generating interest, especially in the neurogenic inflammation models with itch and without flare. More in general there is a great interest in understanding the psycho-neuro-endocrine- immunologic aspects of itch development and its modulation in the setting of the different forms (acute and chronic) of neurogenic inflammation and neural sensitization. This last frontier of the clinical research seems interesting not only for its implicit psycho-somatic consequences in the understanding of neuropeptidergic intractable itch, but mainly for its possible relationship with the intracerebral/ intrapsychic elaboration of some itch-related sensations and mainly of those metaesthesic sensations simply (but imprecisely) described as "itch". New concepts, new interdisciplinary experimental and semiologic models are thus needed for understanding and possibly treating the presently "untractable neuropeptidergic itch".

OP49 PRURITUS IN PSORIASIS: AN UPDATE

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Pruritus seems to be an important symptom of psoriasis, however its role has been neglected during the last decades. Nowadays, we all agree that 70–90% of psoriatic individuals suffers from itch. The intensity of pruritus in this population is not very severe; according to VAS it is assessed as 5.2 to 6.4 points. In about 80% of pruritic subjects pruritus is limited to psoriatic lesions, however in the remaining ones it involves also the non-lesional skin. Pruritus occurs quite commonly both on the trunk and extremities, however face is rarely involved. Additionally, about 44% of psoriatic women report discomfort (pruritus and burning) within the vulvar area. The pathogenesis of psoriatic pruritus remains not completely clear. Our group showed that prevalence and intensity of pruritus in psoriatic individuals may be influenced by the stress. As stress could modulate neurogenic inflammation and pruritus perception the relationships between psoriatic pruritus and rich skin innervation, as well as increased local expression of several neuropeptides, including substance P and calcitonin gene related peptide in psoriatic plaques have been documented. Recently it has been proposed that imbalance in all neuropeptide homeostasis (innervations, neuropeptides and endopeptidase) may play an important role in the pathogenesis of pruritus in psoriatic subjects. Pruritus influences psoriatic individuals' psyche. Itch intensity significantly correlates with degree of quality of life impairment, level of stigmatization as well as presence and severity of depressive symptoms. Moreover, we showed that pruritus is responsible for the decrease of work ability of patients suffering from psoriasis. In conclusion, pruritus is a common and important symptom in psoriasis with a complex pathogenesis markedly influencing patients' psyche.

OP50 AUTOTAXIN IS A POTENTIAL MEDIATOR OF CHOLESTATIC PRURITUS

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Pruritus is a disabling symptom in patients with cholestatic liver disorders. Bile salts and opioids have, among others, been implicated in the aetiology of pruritus, but a relation with itch intensity could never be established. In our laboratory, lysophosphatidic acid (LPA) was identified as neural activator in blood of pruritic cholestatic patients and induced scratching behaviour in mice. In vivo, autotaxin (ATX) is the main source of LPA. Therefore, it was our aim to determine correlation of ATX activity, total bile salts, histamine levels and μ-opioid activity with pruritus in cholestatic patients. **Methods:** Serum of women with intrahepatic cholestasis of pregnancy (ICP; n=31), pregnant controls (PC; n=29), patients with other causes of cholestasis (mainly primary biliary cirrhosis; n=51) and healthy subjects (HC; n=180) was analyzed. Autotaxin activity, histamine concentrations, and bile salts were determined by enzymatic assays, and autotaxin protein by western blotting. μ-opioid activity was assessed by receptor binding assay. **Results:** Similar to LPA concentrations, ATX activity and protein content was markedly and significantly increased in sera of ICP patients vs. PC (2.4-fold; p<0.0001) and in sera from pruritic cholestatic vs. non-pruritic cholestatic patients (1.8-fold, p<0.0001) and vs. HC (2.2-fold, p<0.0001). There was a highly significant correlation (p<0.0001, n=51) between serum ATX activity and intensity of pruritus, as quantified by VAS. In PBC patients who underwent nasobiliary drainage to treat severe pruritus, autotaxin activity decreased significantly and returned to increased levels when drainage was stopped and pruritus had returned. Neither total bile salt concentrations nor histamine levels or μ-opioid activity correlated with itch intensity. **Conclusion:** Our data suggest that autotaxin and its product, LPA, play a key role in cholestatic pruritus. We speculate that currently developed ATX inhibitors may represent a causative therapy of this yet insufficiently treatable perception in cholestasis.

OP51 UREMIC PRURITUS: BILATERAL SYMMETRY AND ITCH-ASSOCIATED MORBIDITY

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Background: Approximately 42-45% of hemodialysis (HD) patients have moderate to extreme itching. Spatial distribution of itching in uremic pruritus (UP) has not been characterized. In this first longitudinal natural history study of UP, we examined spatial patterns of UP and related them to itch-associated signs and symptoms. **Methods:** Standard body diagrams were used. Patients indicated areas of itching and characterized

themselves according to "A, B, C" categories covering 3 domains: 1) scratch marks on skin, 2) problems sleeping due to itching, 3) negative mood due to itching. "A" patients did not have problems in these 3 areas, "B" patients "sometimes" had problems, and "C" patients "often" had problems. **Results:** Among 103 patients enrolled, itching was constant in 31%. In 83% of patients, itching involved large, non-dermatomal areas with striking bilateral symmetry. Among the C (most severe) category patients, 96% (24/25) had bilaterally symmetric itching. Dialysis adequacy was better than the recommended U.S. National Kidney Foundation (NKF) target among patients in all 3 categories, and no measured laboratory parameters (Hb, calcium, phosphate, PTH, etc) distinguished the groups. **Discussion:** UP is characterized by large, bilaterally symmetric areas of itching, associated with frequent sleep and mood disturbances. The pattern of bilateral symmetry supports a prominent central neurogenic component in maintenance of UP, perhaps recalling the common origins of nervous system and skin from ectodermal primordia. Of note, in a similarly symmetric itch condition, atopic dermatitis, Yosipovitch found bilateral brain activation after unilateral administration of a pruritogen (histamine iontophoresis) using Arterial Spin Labeled fMRI. In normal volunteers, unilateral histamine led almost exclusively to unilateral brain activation during itching. We hypothesize that chronic "itch-scratch" cycles lead to central neuroplastic changes, such that even a unilateral itch stimulus is processed bilaterally in brain, resulting in symmetry of itch sensation on the skin as well as amplified itch intensity.

OP52 SERUM CONCENTRATIONS OF SUBSTANCE P ARE INCREASED IN CHOLESTASIS: POTENTIAL CLINICAL IMPLICATIONS

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Background: Substance P (SP) is an excitatory neuropeptide, which is associated with hyperalgesia (i.e. increased sensitivity to noxious stimuli). Experimental data from rats indicate that sustained opiate administration (i.e. increased opioidergic tone) activates mechanisms that promote pain, mediated, in part, by the NK-1 receptor. The increased opioidergic tone of cholestasis may contribute to a state of enhanced nociception, also mediated by SP, and perceived as pruritus. We hypothesized that cholestasis is associated with increased neurotransmission via SP, mediated, in part, by its increased availability. Accordingly, the aim of this study was to determine the serum concentrations of SP in patients with chronic liver disease with and without pruritus. **Patients:** Twelve subjects were control, 17 had chronic liver disease (CLD) without pruritus (i.e. disease control group), and 14 had CLD and pruritus. The study was approved by the institutional review board, and consent was obtained from all the patients. **Methods:** Serum SP concentrations were measured by a competitive enzyme immunoassay (Cayman Chemical Company). A statistical significance was sought by the unpaired *t*-test. **Results:** SP concentration (mean±SD) in patients with CLD with pruritus was 9.49 pg/ml±6.87, in patients with CLD without pruritus it was 0.75 pg/ml±0.77, and in the control group it was 0.78 pg/ml±0.48. The differences between the three groups were significant ($p < 0.0002$). **Summary:** Mean serum SP levels were significantly higher in patients with CLD and pruritus than in the disease and the control groups. **Conclusions:** In patients with cholestasis and pruritus there is increased availability of SP. **Speculation:** Increased neurotransmission mediated by SP may contribute to the pathophysiology of cholestasis, including pruritus. The study of SP antagonists to treat the pruritus of cholestasis merits exploration.

OP53 THERAPEUTIC STRATEGIES IN CHRONIC PRURITUS WITH SYSTEMIC DISEASE

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Pruritus with systemic disease (PsD) is a frequent and often tormenting symptom in patients with various mostly internal diseases. In many cases PsD is difficult to overcome. While treating the underlying pathology (for instance stenting of an obstructive bile duct) instantly resolves the itch this is not applicable in other circumstances and PsD often becomes a therapeutic riddle. In these cases different medical and other therapeutic approaches are adopted with mostly partial success. Recently administration of high dose antihistamines have yielded good results in pruritus of patients with various diseases. Similarly some of the newer antidepressive drugs as paroxetine and sertraline) proofed to be effective in PsD. In advanced or endstage liver disease albumin dialysis (i.e. MARS) although costly is reported to alleviate tormenting pruritus in desperate cases. Mu-receptor-antagonistic and kappa-agonistic drugs have been reported to reduce pruritus in kidney and other diseases. A few reports deal with the effectiveness of neuropeptides in the treatment of pruritus, however the results are mediocre at best. We are still waiting for therapeutic instruments aimed directly against the culprit leason in PsD, but at present knowledge of the underlying pathophysiology is mostly speculative.

OP54 THERAPEUTIC ADVANCES IN TREATING ITCH

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The treatment of inflammatory skin conditions associated with itch has been primarily managed by decreasing the inflammation using agents including topical corticosteroids and calcineurin inhibitors. These agents indirectly affect the itch process and mediators themselves. In inflammatory allergic itch, topical cromolyn has been investigated and has modest efficacy. Novel agents to block the inflammatory process are under investigation, including SRD441, a protease inhibitor with a unique mechanism of action and TS-022, a prostanoid DP_1 receptor agonist. In contrast to the inflammation, therapeutic approaches to decrease the sensation of itch have been more challenging, and several approaches have been or are currently being investigated. These approaches include systemic and topical opioid antagonists such as naltrexone and SRD174. Oral opiate antagonists have some data suggesting effect. This talk will show new approaches for treating itching.

OP55 RESULTS OF A CLINICAL STUDY FEATURING THE SENSORY EVALUATION, ON HUMANS, OF THE ANTIPRURITIC EFFECT OF A TOPICAL SUPEROXIDE DISMUTASE

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Objective: To evaluate the antipruritic effect of topical SOD versus non treated zone. **Methodology**: Randomized and intra-individual study. **Assessment criteria**: Measure of the Cutaneous Thermal Sensitivity (CTS) with the TSAR. **Kinetics**: D0t0, t30', t90'. **Methodology**: Treated zone/Non-treated zone. Zone: Wrists. **Application frequency**: One standardized application (2 µl/cm^2). **Results–Conclusion**: Under these study conditions, topical Superoxyde Dismutase presented a significant antirpuritic effect 30 min and 90 min after the product application, in comparison to the initial values and to the non-treated zone. This effect is characterized by: – a decrease in the number of subjects who presented a pruritus after the investigational product application, – a significant decrease in the length of the pruritus and a significant increase in the beginning of the pruritus (on the subjects who presented a pruritus) on the treated zone 30 min after the product application, – a significant decrease in the pruritus intensity (on the subjects who presented a pruritus) on the treated zone 90 min after the product application.

OP56 A RANDOMIZED, MULTICENTER TRIAL OF TOPICAL TACROLIMUS FOR TREATMENT OF PRURITUS IN PATIENTS WITH ATOPIC DERMATITIS

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Background: Controlling pruritus is important in the treatment of atopic dermatitis (AD). However, pruritus of AD is not readily controlled with the standard topical steroid therapy. Anti-pruritic effects by topical calcineurin inhibitors have been reported, but not well-determined yet. **Objective:** The purpose of the study was to better-examine the anti-pruritic efficacy of topical tacrolimus monotherapy in the treatment of AD. **Patients and Methods:** Seventy patients with AD were recruited except for those who had been treated with orally-administered corticosteroids, cyclosporine and antihistamines within 2 weeks prior to the start of TEST-1. In TEST-1, all the patients received topical tacrolimus and emollients twice daily with minimum amounts (<20 g/2 weeks) of topical corticosteroids for 2–4 weeks, and change of VAS-itch score and severity of disease were examined. Patients who showed reduced visual analogue scale (VAS)-itch score by more than 20 points further proceeded to TEST-2, divided into two groups; the first one continued topical tacrolimus monotherapy, while the other received only emollients. In TEST-2, topical corticosteroids were not allowed to apply. **Results:** Sixty-eight patients completed TEST-1, and 44 out of 68 patients showed relief of pruritus (64.7%) by the topical tacrolimus + low dose topical corticosteroids combination treatment. Forty-two out of these 44 responding patients completed TEST-2, and recurrence of pruritus, defined by more than 20 points-increase of VAS-itch score, occurred in only 5 out of 21 in tacrolimus monotherapy group while it did so in all the patients in emollient group. The median days for recurrence was >28 days in tacrolimus monotherapy group and 3 days in emollient group, respectively. **Conclusions:** Relief of pruritus was observed by topical tacrolimus + low-dose topical corticosteroids combination therapy in most of patients with AD. In these responding patients, sequential topical tacrolimus monotherapy was found significantly effective in controlling pruritus of AD.

OP57 EFFICACY OF SWEAT-ANTIGEN-INACTIVATING SPRAY ON ITCHING OF PATIENTS WITH ATOPIC DERMATITIS

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Background: Many patients with atopic dermatitis showed immediate-type hypersensitivity against sweat antigen. Therefore, to deal with sweating is important to prevent itching and aggravations of dermatitis of patient with atopic dermatitis. **Objectives:** To find a substance that inactivates sweat antigen and its efficacy when used as an aerosol spray for patients with atopic dermatitis. **Methods:** Tannic acid (JP) was selected by screening of various natural products and administered in an aerosol spray on 18 patients with atopic dermatitis at least once a day for 4 weeks in a cross-over, double-blind study. Clinical severity of atopic dermatitis and degrees of itching in daily life of patients were evaluated by physicians and patients themselves, respectively. **Results:** Degrees of itching in morning and those at night were significantly more largely improved by the use of tannic acid-containing spray than those by the use of placebo containing spray. The overall efficacy of tannic acid-containing aerosol sprays was also significantly higher than those of tannic acid-free spray. **Conclusion:** Sweat-antigen-inactivating spray may be effective to reduce itching of patients with atopic dermatitis.

OP58 PSYCHOGENIC PRURITUS

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We would like to propose some opinions about the following questions: Does psychogenic pruritus exist? How could we define it? Are "functional itch disorder" or "somatoform itch" more appropriate words? How can we understand it? Are there similar disorders? Is it related to pleasure? How can we give this diagnosis to a patient? What about the treatment? In our opinion, psychogenic pruritus exists, is different from the aggravation of itch from other origins aggravated by psychological factors and it is necessary to not mingle them. The major role of brain in itch explains its pathophysiogeny.

OP59 PSYCHOSOMATIC ASPECT AND ITCH IN PATIENTS WITH ATOPIC DERMATITIS

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Atopic dermatitis is a well-known psychosomatic skin disorder in Japan. In our research, patients with this disease were found to be more depressive and psychosomatic symptom-prone than controls. In terms of anxiety, however, no statistically significant correlation was seen between patients and controls. It may be because that most patients in this disease we sampled are in their adolescent. Healthy adolescent also has anxiety in general. Patients with moderate symptoms tend to be more depressive and psychosomatic symptom-prone than controls. They also tend to be more depressive mood than patients with mild symptoms. Management of itch and scratch is an important problem in atopic dermatitis. Our research revealed that psychological education and habit reversal techniques have an effect on improving skin symptom and increasing self-care behaviors. Recently we investigated itch and anxiety in patients with atopic dermatitis. Patients significantly have higher scores than healthy controls in anxiety to itch and in scratching. Scratching of patients with atopic dermatitis has negatively affected to mental aspects, such as social functioning and mental health in short form(SF)36. Scratching affected by anxiety to itch may influence the depression and the disturbance of a social function in patients with atopic dermatitis.

OP60 PSYCHOLOGY OF ITCH – SOMATOFORM PRURITUS

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Itch is a common bodily sensation which is mostly influenced by subjective behaviour and psychological comorbidities are common in the clinical evaluation of patients. In a psychosomatic meaning itch is as well a bodily aspect as also have mental complaints and is mentally inducible (Niemeier et al. 1999). New aspects of mentally induced itch in atopic dermatitis subjects show the psychological influence of this itch behaviour and will presented. The somatoform itch (Stangier et al. 2003) is a somatoform disorder with pruritus as diagnosed in the DSM-IV or ICD-10 respectively. A study from Stangier and Gieler (1997) in a university outpatient department showed that 6.5% of the dermatological outpatients had somatoform pruritus. The therapeutic concepts of somatoform disorders will probably help to manage patients with 'psychogenic pruritus'. For psychosomatic aspects a psychological comorbidity of depression, anxieties and personality disorders should be recognized (Gupta et al 1994). The comorbidity of pruritus and depression was shown in a study by Sheehan-Dare et al. (1990) showed a high correlation of pruritus and depression in comparison to healthy controls. Psychiatric patients showed a high prevalence of pruritus in a cohort study by Picardi et al. (2000), when showing that 30% have a comorbidity of pruritus. The influence of stress in itch is highly correlated with regard to the subjective answers in a population based study of Oslo (Dalgard et al. 2007). There are some first therapeutic studies in atopic dermatitis itch with education intervention which showed the decreasing effect of itch-scratching control behaviour techniques (Kupfer et al. 2009).

OP61 A MULTIDISCIPLINARY TRAINING PROGRAMME FOR PATIENTS WITH CHRONIC PRURITUS

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Chronic pruritus (> 6 weeks) is a worldwide symptom and a burden in many dermatological, systemic and psychosomatic/psychiatric diseases. Patients with chronic pruritus frequently endure a long and complicated disease course, failure of therapy and a substantial reduction in quality of life. Psychological mechanisms may be involved in eliciting and coping with chronic pruritus. Treatment of pruritus aims to be aetiological, but as a primary illness it is symptomatic. The needs of patients with chronic pruritus are diverse. Multidisciplinary educational and psychological training programmes aim to improve patients' understanding of the disease, raise motivation to apply more adaptive self-care measures, and consequently improve quality of life. A multidisciplinary training consisting of dermatological, health-educational and psychological modules and based on the needs of patients with chronic pruritus was developed. The programme comprises four weekly meetings lasting two hours each and has been offered to 41 individuals so far. The programme provides information about the medical fundamentals of the skin, the multi-factorial nature of pruritus, current diagnostic procedures, the epidemiology of pruritus and therapeutic avenues for the relief of pruritus. Patients also learn about and discuss more adaptive behavioural response patterns to pruritus and the interrelationship between stress and pruritus. An established relaxation technique is practised. During all modules patients are encouraged to share their experiences with other patients. Maintenance of health through educational programmes, such as the one presented here, can be considered important complementary measures in the field of medicine and psychosomatics, which should also be applied to patients with chronic pruritus. Patients rated the programme as a highly expedient means to increase their understanding of pruritus and felt empowered to better deal with the pruritus sensation in daily life.

OP62 SUICIDAL IDEATION IN ITCH

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Purpose: Suicidal ideation is associated with suicide attempts, depression and bodily pain. The relation between suicide ideation and the symptom itch is not explored previously. Itch is the most widespread symptom of chronic skin disease. The objective of the present study is first to describe an expected association between suicidal ideation and pain in adolescents and then explore if suicidal ideation and itch is associated. **Methods:** 4,744 adolescents were invited to a questionnaire-based population study. The participation rate was 80%. Suicidal ideation, itch, negative life events and mental distress were all self-reported variables. **Results:** A dose/response relationship was seen between suicidal ideation and itch. The crude association between severe itch and suicidal ideation showed an odds

ratio of 4.7 (95% CI: 2.5–8.9) in boys and 2.5 (95% CI: 1.6–3.8) in girls and remained significant in the adjusted analyses among boys with an odds ratio of 2.7 (95% CI: 1.3–5.7). **Conclusion:** Itch is associated with suicidal ideation among adolescents in the general population in Oslo, Norway. These results add to the description of the burden of the symptom itch and should be explored further.

OP63 OPIOIDS AND ITCH: CENTRAL AND PERIPHERAL MECHANISMS

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It is common knowledge that pain reduced itch. Also the opposite is true: reduction of pain by opioids can cause itch. Mu-opioids given close to the spinal cord are analgesic, but cause segmental itch, i.e. they provoke itch on the spinal cord level without input from primary afferent fibers. Interestingly, kappa-opioids, albeit also being analgesic, have been shown to act antipruritic. Thus, on spinal cord level analgesic and pruritic/antipruritic effects of opioids are complex and the exact neuronal circuits that underlie differential pruritic/antipruritic effects of mu- and kappa opioids in the spinal cord are not identified. In the periphery, however, even the main effects of opioids are not entirely clear. Mu- and kappa opioid receptors have identified on neurons and keratinocytes and higher expression of mu- vs. kappa opioids and their receptors have been suggested to favour the development of chronic itch. The existence of opioid signalling in the skin is obvious, but there is an ongoing debate on the specific role of the different opioid receptors not only on neuronal excitation or inhibition, but also on cell differentiation, immuno-modulation and skin barrier function. Defining the role of opioids for chronic pruritus in the periphery is therefore complicated by the necessity to not only include the direct neuronal effects, but also to take into account the complex local non-neuronal signalling modulating skin barrier function, keratinocyte differentiation and inflammatory activity of immune cells that also may contribute to induction and maintenance of chronic itch.

OP64 PHARMACOLOGICAL PROPERTIES OF NALFURAFINE, A NOVEL ANTIPRURITIC AND KAPPA-OPIOID RECEPTOR AGONIST

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Nalfurafine hydrochloride is a novel derivative of the opioid receptor antagonist, naltrexone. Investigation of non-clinical in vitro pharmacological studies revealed that nalfurafine hydrochloride was a potent and selective agonist for human kappa-opioid receptors without any appreciable action on mu- or delta-opioid receptors. In non-clinical in vivo pharmacological studies, nalfurafine hydrochloride inhibited the intradermal histamine- or substance P-induced scratching behavior in mice and other various pruritic models in mice, rats, or monkeys, suggesting that nalfurafine hydrochloride possesses the potential for the therapeutic amelioration of various types of pruritus. Nalfurafine hydrochloride had little or no inhibitory effect on inflammatory mediators and no appreciable affinity for various receptors; the scratching inhibitory effect of nalfurafine hydrochloride was antagonized by subcutaneous and intracerebroventricular administration of nor-BNI, a kappa-opioid receptor antagonist. Therefore, it was indicated that nalfurafine hydrochloride could produce its antipruritic effect via central kappa-opioid receptor activation, not by any other mechanisms. Since nalfurafine hydrochloride is an opioid drug, the abuse potential was then assessed in rats and monkeys. Nalfurafine hydrochloride showed slight physical dependency in rats. However, in a self-administration study in monkeys, no reinforcing effect was observed in nalfurafine hydrochloride, suggesting that nalfurafine hydrochloride has no abuse potential. From these findings, it is concluded that nalfurafine hydrochloride possesses the potential for the therapeutic amelioration of various types of pruritus including uremic pruritus of hemodialysis patients with no abuse liability. A new drug application of the oral formulation of nalfurafine hydrochloride was filed to Japanese health authority in November, 2006, and it was approved in January, 2009.

OP65 EFFECT OF A NOVEL KAPPA-RECEPTOR AGONIST, NALFURAFINE, FOR SEVERE ITCH IN 337 HEMODIALYSIS PATIENTS: PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

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Background: Pruritus in hemodialysis patients is an intractable disease and substantially impairs their quality of life. Based on results of our earlier clinical study, we hypothesized that the μ (mu) opioid system is itch-inducible, whereas the κ (kappa) system is itch-suppressive. **Patients and Methods:** The efficacy and safety of nalfurafine hydrochloride (a novel kappa receptor agonist) were prospectively investigated by randomly administering 5 μg or 2.5 μg of the drug or a placebo orally for 14 days using a double-blind design in 337 hemodialysis patients with itch that was resistant to currently available treatments, such as antihistamines. **Results:** The mean decrease in visual analogue scale (VAS) from baseline, the study's primary endpoint, was significantly larger in the 5-μg nalfurafine hydrochloride group (n=114) than in the placebo group (n=111, p=0.0002, one-sided test at 2.5% significance level). The mean decrease in the VAS in the 2.5-μg group (n=112) was also significantly larger than that in the placebo group (p=0.0001). The incidence of adverse drug reactions (ADRs) was 35.1% in the 5-μg group, 25.0% in the 2.5-μg group, and 16.2% in the placebo group. Moderate to severe ADRs were observed in 10 of the 226 patients. The most common ADR was sleep disturbance, seen in 24 of the 226 nalfurafine patients. **Conclusions:** This Phase III, randomized, double-blind, placebo-controlled, parallel-group, prospective study based on VAS evaluations clearly showed that orally taken nalfurafine hydrochloride effectively reduced itches that were otherwise refractory to currently available treatments in maintenance hemodialysis patients, with few significant ADRs. This novel drug is now being widely used, after official approve (January 2009) by the Ministry of Health, Labour and Welfare of Japan.

Poster Abstracts (PB01-PB21 and PC01-PC22)

PB01 EVALUATION OF RESIDUAL SEDATIVE EFFECT OF ANTIHISTAMINES BY MEASURING CENTRAL HISTAMINE H1 RECEPTOR OCCUPANCY USING 11C-DOXEPIN-PET

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Antihistamines are often used as the first-line treatment for relieving the symptom of itch. Although they are clinically effective, they sometimes produce significant sedation and impaired performances. Antihistamines exert their sedative effect by blocking central histamine H1 receptors (H1Rs). We have achieved to objectively evaluate the sedative property of antihistamines by measuring the central H1R occupancy (H1RO) using positron emission tomography (PET) and 11C-doxepin. But up to now, the residual sedative effect of these drugs on the next day is rarely evaluated, despite of the fact that sedative antihistamines are often advised to be taken before sleep, and some of them are frequently used OTC drugs as sleep aid. The primary aim of this study is to evaluate the residual sedation intensity of diphenhydramine and bepotastine on the next day, by measuring central H1RO 12 h after oral drug administration. We ultimately aim to provide useful information on the remnant sedative side-effect of frequently used antihistamines, especially, the OTC drugs. Eight healthy male adult subjects who took bepotastine 10mg (Talion), diphenhydramine 50 mg (Drewell) or placebo (7-day intervals between drug treatments) orally in the previous night (23:00) received a PET scan on the next morning (11:00). The H1RO were calculated in several brain regions. We found BEP occupied about 15.4% of H1 receptors in brain, while DIP occupied 45.4%, even at 12 h post-drug. This result suggests that BEP, with its relatively low H1RO, thus minimal contribution to cognition decline in the next morning, serves well as a non-sedative antihistamine. On the contrary DIP remains predominant sedative effects due to its relatively high central H1RO even 12 h after it is orally taken. This should draw our attention on the possible residual cognitive decline and impaired performance even though we use sedative drugs at night.

PB02 OLOPATADINE HYDROCHLORIDE INHIBITS SCRATCHING BEHAVIOR INDUCED BY A PROTEINASE-ACTIVATED RECEPTOR 2 AGONIST IN MICE

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The proteinase-activated receptors 2 (PAR2) is highly expressed in the skin and is activated by trypsin, mast cell tryptase, and synthetic PAR2 agonists, such as SLIGRL-NH2. Tryptase and PAR2 are up-regulated on sensory nerves in the skin from atopic dermatitis patients. Indeed, intradermal injections of SLIGRL-NH2 evoke dose-dependent scratching in mice. In addition, PAR2 agonists induce the release of neuropeptide, such as substance P (SP), from primary afferent neuron. Pretreatment of mice with a histamine H1 receptor antagonist, pyrilamine, has no effect on PAR2-mediated scratching. These results indicate that PAR2 signaling induces itching independently of histamine H1 receptor signaling. Olopatadine is a second-generation antihistamine. Olopatadine inhibits ear swelling and cytokine production in a murine chronic contact hypersensitivity model, while other antihistamines do not suppress them, suggesting that olopatadine exerts additional biological effects besides its blockade of histamine H1 receptor. In this study, we examined the effect of olopatadine on PAR2 agonist-induced scratching behavior in mice. The PAR2 agonist induced scratching behavior just after the administration and its effect continued until 30 min after the administration. Pretreatment with olopatadine significantly decreased the number of scratching behavior. Olopatadine also inhibited elevation of plasma SP levels induced by the PAR2 agonist treatment. Furthermore, SP treatment induced scratching behavior, which was inhibited by olopatadine pretreatment. Many studies have shown that olopatadine has various pharmacological and biological activities besides its histamine H1 receptor antagonistic activity. In this study, olopatadine inhibited the PAR2 agonist-induced SP secretion. Furthermore, olopatadine decreased SP-induced scratching behavior. Collectively, the inhibitory effect of olopatadine on the PAR2 agonist-induced itching may be related to the inhibition of SP release and SP-induced itching by olopatadine, which is downstream of PAR2 signaling. Furthermore, the significant inhibitory effect of olopatadine on the PAR2 agonist-induced itching suggests that olopatadine may be effective for H1 antihistamine-resistant itching.

PB03 THE EFFECT OF YOKUKANSAN ON ATOPIC DERMATITIS-LIKE LESIONS IN SOCIALLY ISOLATED NC/NGA MICE

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Pruritus is a characteristic symptom in various forms of dermatoses, especially in atopic dermatitis (AD). It is known that mental stress can trigger itch sensation, and thus exacerbate symptoms of AD. Psychotherapy is becoming more important especially in the treatment of severe AD patients. In the present study, we investigated the effect of Yokukansan (YKS), a traditional Japanese medicine, on AD-like dermatitis in NC/Nga mice, in which AD-like skin lesions develop spontaneously. YKS has been utilized in the treatment of neurosis, insomnia, anxiety, night cry of children, and so forth. 10-week-old male NC/Nga mice were socially isolated under conventional conditions. YKS was administered orally to mice together with diet for 12 weeks at the dosage of 0.6 g/kg or 1.2 g/kg body weigh per day. The efficacy of YKS was evaluated by assessing skin lesion severity, scratching behavior, grooming behavior, skin hydration, and infiltration of inflammatory cells in the skin. In addition, the serum corticosterone, total IgE and nerve growth factor (NGF) levels were measured. YKS significantly suppressed dermatitis scores, scratching behavior and grooming

behavior, infiltration of mast cells and eosinophils in the skin, and improved the retention of humidity in the skin in a dose-dependent manner. There were no significant differences in the levels of serum total IgE and NGF between the YKS-treated mice and the non-treated control mice. Serum corticosterone levels were decreased in the 1% YKS-treated mice as compared with those of the control mice. These results suggest that YKS possesses an anti-itching property, which might be due to the alleviation of social isolation stress. Thus, it is expected that YKS might provide an effective alternative therapy for AD in human patients.

PB04 DEVELOPMENT OF A NOVEL MOUSE ATOPIC DERMATITIS MODEL INDUCED BY MITE FECAL ANTIGEN

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Introduction: Atopic dermatitis is defined as a chronic and relapsing eczematous dermatitis with severe itching. Mite antigen plays important roles in the onset and development of atopic dermatitis and breakdown of the epidermal barrier system due to inflammation and scratching. To understand the onset and development of a disease, appropriate animal models are essential. Previously, we reported an atopic dermatitis model caused by repeated topical application of *Dermatophagoides farinae* crude extract in NC/Nga mice. However, scratching behavior could not be observed in the previous model in spite of the dermatitis skewed to Th2. In the present study, therefore, we attempted to establish a model with frequent scratching behavior by painting with mite fecal antigen (FAg) on to the ear lobes in NC/Nga mice. **Methods:** FAg was prepared from feces of *D. farinae* kept in our laboratory. FAg solution was painted onto the ear lobes of NC/Nga mice 9 times at twice a week. Ear swelling was measured using a dial thickness gauge before, and 1, 2, 4, 8, 12, 24, 48 and 96 h after each mite antigen application. Scratching behavior was estimated for 1 h immediately after each FAg challenge using MicroAct. Total IgE levels in sera obtained from mice 24 h before each FAg challenge were measured and histological images in ear lobes at 24 h after the last challenge were analyzed. Effects of tacrolimus and dexamethasone on the dermatitis were also examined. Tacrolimus and dexamethasone were treated once a day from the day of 5th challenge. **Results:** Severe dermatitis with infiltration of inflammatory cells and elevated serum IgE levels were induced by repeated topical application of FAg. Moreover, frequent scratching behavior was by the FAg application from 4th antigen challenge. Both tacrolimus and dexamethasone suppressed inflammation and scratching behavior apparently.

PB05 INHIBITORY TRANSMITTERS MEDIATING SCRATCH-EVOKED INHIBITION OF SPONTANEOUSLY ACTIVE SPINAL DORSAL HORN NEURONS IN A MOUSE MODEL OF CHRONIC DRY SKIN ITCH

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We presently investigated if spontaneous activity of superficial dorsal horn neurons is inhibited by scratching in a mouse dry skin chronic itch model. We also tested if scratch-evoked inhibition was reduced by antagonists of GABA and glycine. Finally, we assessed the role of a supraspinal loop in scratch-evoked inhibition by determining if the latter was reduced by disruption of the upper cervical cord. Chronic dry skin on the hind paw of adult ICR mouse was created by twice-daily treatment with acetone and diethyether (1:1) followed by water. After 10 treatment days, mice were anesthetized with pentobarbital and spontaneously active single units recorded in superficial lumbar dorsal horn. Repetitive scratches (2 Hz) were applied to the hind paw with a brush bristle for 1 min, before and 1 min after a 30-sec period of superfusion of the dorsal spinal cord surface with the GABA-A antagonist bicuculline (20 μM), the GABA-B antagonist saclofen (100 nM), or the glycine antagonist strychnine (4 μM). Scratching was also tested before and during application of saline ice to the dorsal upper cervical cord. Thirty-five superficial units (34 mechanically insensitive, 1 wide dynamic range) exhibited ongoing firing (8–12 Hz). Spontaneous firing was significantly reduced during scratching (to 52% of pre-scratch baseline; $p<0.001$ paired *t*-test). The degree of scratch-evoked inhibition was significantly less during application of bicuculline (to 85.2%, $n=14$ units), saclofen (to 77.3%; $n=12$) and strychinine (to 94.2%, $n=8$). Upper cervical cold block or complete spinalization reduced the degree of scratch-evoked inhibition (to 64%). Suppression of neuronal firing by scratching may underlie its antipruritic effect. The marked attenuation of scratch-evoked inhibition of neural activity by GABA-A, GABA-B and glycine antagonists supports a role for these spinal inhibitory neurontransmitters in the antipruritic effect of scratching. A descending antipruritic pathway might be partially involved in this effect.

PB06 DISTINCT SCRATCHING AND WIPING BEHAVIORS ELICITED BY INTRADERMAL INJECTION OF PRURITOGENS OR ALGOGENS INTO THE CHEEK OF MICE AND M-OPIOID MODULATION

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We investigated the ability of a mouse model to distinguish between behavioral responses to itch (hindlimb scratching) and pain (forelimb wiping) elicited by id injection of pruritogens or algogens into the cheek. We also investigated μ-opioid modulation of scratching and wiping responses. Adult ICR mice received unilateral id cheek injection (10 μl) of saline or 7% Tween80 (vehicles), pruritogens histamine (35–50 μg), PAR-2 agonist SLIGRL-NH2 (35–50 μg), 5-HT (0.03–0.1%), and PAR-4 agonist AYPGKF-NH2 (35–50 μg), or the algogens capsaicin (10-30 μg) and mustard oil (0.01–0.1%), and then videotaped. Hindlimb scratch bouts and ipsilateral forelimb wipes directed to the injection site were counted at 5-min intervals for 40 min. Single heat-inactivated cowhage spicules soaked with histamine (10 mg/ml) or capsaicin (200 mg/ml), or native cowhage spicules, were inserted into the cheek using forceps. Morphine (0.1-1 mg/kg ip) or naloxone (1 mg/kg, sc) was given 10 min prior to id injection of histamine (50 μg) or capsaicin (30 μg). Each pruritogen elicited dose-related increases in numbers of scratch bouts with few wipes. Capsaicin and mustard oil elicited dose-related increases in wipes with few scratches. The cowhage spicule elicited equal numbers of scratches and wipes, the histamine-soaked spicule elicited more scratches than wipes, and the capsaicin-soaked spicule elicited more wipes than scratches. All evoked responses were significantly

greater compared to controls receiving an inactivated untreated spicule. Morphine significantly inhibited capsaicin-evoked wiping, but not histamine-induced scratching. Naltrexone significantly decreased histamine-induced scratching, but not capsaicin-evoked wiping. Pruritogens elicited primarily scratching that was reduced by a μ-opioid antagonist, while algogens primarily evoked wiping that was suppressed by morphine, suggesting that scratching and wiping reflect itch and pain, respectively. Cowhage elicited signs of both itch and pain, consistent with human sensations. The cheek injection method represents a useful animal model to distinguish between facial itch and pain.

PB07 EXCITATION OF MOUSE SUPERFICIAL DORSAL HORN NEURONS BY HISTAMINE AND/OR PAR-2 AGONIST: POTENTIAL ROLE IN ITCH

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Recent studies suggest the existence of separate transduction mechanisms and sensory pathways for itch elicited by histamine, or by spicules of cowhage that evoke histamine-independent itch. The latter is mediated partly via protease-activated receptor subtype-2 (PAR-2). We investigated if histamine and the PAR-2 agonist, SLIGRL-NH2, excite distinct sub-populations of neurons in the superficial dorsal horn of mice. Single units were recorded in superficial lumbar dorsal horn of adult ICR mice anesthetized with pentobarbital. Unit activity was searched using a small intradermal (id) hindpaw injection of histamine or SLIGRL-NH2. Isolated units were subsequently challenged with id histamine followed by SLIGRL-NH2 (each 50 μg/1 μl) or reverse order, followed by presentation of mechanical, thermal and algogenic stimuli. Forty-three units were classified as wide dynamic range (62%), nociceptive-specific (22%) or mechano-insensitive (16%). Twenty-one units gave prolonged (mean 13 min) discharges to the first id injection of histamine; 76% also responded to subsequent SLIGRL-NH2. These units also responded to noxious heat (63%), cooling (43%), topical mustard oil (56%) and id capsaicin (67%). Twenty-two other units gave prolonged (5 min) responses to initial id injection of SLIGRL-NH2; 85% also responded to subsequent id histamine, albeit more weakly. They also responded to noxious heat (75%), mustard oil (93%) and capsaicin (75%) and one to cooling. Responses to histamine were smaller when tested after SLIGRL-NH2, compared to when histamine was tested first. Similarly, SLIGRL-NH2-evoked responses were weaker post-histamine compared to when SLIGRL-NH2 was injected first, indicating cross-tachyphylaxis between these itch mediators. Many but not all superficial dorsal horn neurons were excited by both histamine and the PAR-2 agonist, suggesting both overlapping and separate pathways for histamine- and non-histamine-mediated itch. Since the large majority of pruritogen-responsive neurons also responded to noxious stimuli, itch may be signaled primarily by a population code rather than a pruritogen-specific labeled-line pathway.

PB08 ITCH-INHIBITORY SYSTEM MEDIATED BY ACTIVATION OF A-ADRENOCEPTORS IN THE SPINAL CORD

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Descending noradrenergic system inhibits transmission of pain signals in the spinal dorsal horn. In this study, we investigated whether itch signals are also regulated by the descending noradrenergic system. Mice were given an injection of serotonin, as a pruritogen, into the hind paw and biting of the injected paw was observed as itch-related behavior. Pretreatment with intrathecal 6-hydroxydopamine, which decreases catecholamine in the spinal cord, enhanced the itch-related behavior. Intrathecal injections of phenylephrine (α_{1A}-, α_{1B}- and α_{1D}-adrenoceptor agonist) and clonidine (α_{2A}-, α_{2B}- and α_{2C}-adrenoceptor agonist) produced a dose-dependent inhibition of the itch-related behavior without effects on spontaneous activity. An intrathecal injection of the nonselective α-adrenoceptor antagonist phentolamine enhanced the itch-related behavior. In contrast, intrathecal injections of prazosin (α_1-, α_{2B}- and α_{2C}-adrenoceptor antagonist) and yohimbine (α_2-adrenoceptor antagonist) did not affect the itch-related behavior. Clonidine-induced inhibition was antagonized by yohimbine, but not prazosin. Moreover, an intrathecal injection of oxymetazoline (α_{1A}- and α_{2A}-adrenoceptor agonist) produced a dose-dependent inhibition of itch-related behavior. These results suggest that descending noradrenergic system inhibits spinal itch transmission through synergic actions on α_1- and α_{2A}-adrenoceptors.

PB09 DEVELOPMENT OF ATOPIC DERMATITIS MODEL AND EFFECTS OF ACTINIDIA EXTRACT ON DERMATITIS IN NC/NGA MICE

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Atopic dermatitis is a chronic itchy, inflammatory skin disease that usually relapses. Although the etiology of atopic dermatitis remains unclear, it has been shown that both Th1 and Th2 cytokines play pathogenic roles in the generation of atopic dermatitis. DA-9102 is a fraction from Actinidia species containing an immune modulating activity for allergy related disease. We have developed the atopic dermatitis model of NC/Nga mice using DNCB and examined wheather DA-9102 suppresses the development of atopic dermatitis-like skin lesions in NC/Nga mice. NC/Nga mice were challenged with DNCB during 5 weeks to develop atopic dermatitis-like skin lesions. Then daily DA-9102 or cyclosporine A or HPMC (control) were given per orally. The efficacy of DA-9102 in NC/Nga mice was judged by measurement of skin lesion severity (modified SCORAD score), serum IgE, IgG2a levels and cytokines (IFN-γ, IL-4) from spleen cells cultured with ConA. Atopic dermatitis-like lesions could be developed in NC/Nga mice by using DNCB topically. Oral administration of 100 mg/kg DA-9102 significantly suppressed the development of dermatitis analyzed by modified SCORAD score ($p<0.01$). The serum IgE level increased gradually with age, but treatment with DA-9102 suppressed the increment of serum IgE level ($p<0.01$). Mean values of IFN-γ in NC/Nga mice of DA-9102 group were lower than those of control mice group ($p<0.05$). Mean values of IL-4 were undetectable in all experimental groups. Serum IgG2a level were not significantly different among all experimental groups. We successfully developed atopic dermatitis model in NC/Nga mice. Based on our *in vitro* data, we suggest that DA-9102 can be useful for the treatment of atopic dermatitis.

PB10 SCRATCHING AND SPINAL C-FOS EXPRESSION IN MICE PERIPHERAL OR CENTRAL ITCH MODELS

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Introduction: Mounting evidence in recent years suggests that a subclass of C-nociceptors, which is mechano-insensitive and histamine-sensitive, and spinothalamic lamina I neurons are involved in generation and transmission of itch signals. Itch is known to be divided into two major types: peripheral itch and central itch. At present, little and no data are available regarding spinal dorsal horn neuron activation in animal models of peripheral and central itch, respectively. We therefore compared central itch with peripheral itch, concerning spinal Fos expression in mice. **Methods:** [Central model] Morphine at a very low dose (0.3 nmol in a volume of 5 µl) was injected into the cerebellomedullar cistern. [Peripheral models] Compound 48/80 (100 µg/50 µl) was injected intradermally into the rostral part of the back. To assess the dorsal horn neuron activation, Fos-like immunoreactive (Fos-LI) neurons was quantified. Thirty min after intracisternal morphine (M group) or vehicle (control group), or intradermal compound 48/80 (C48 group) or vehicle (control group), the mice were transcardially perfused with phosphate buffer saline. The spinal cord at the Th6-7 level was dissected, immunostained for Fos protein, and quantitatively analyzed for Fos-LI neurons. All Fos-LI neurons in the superficial laminae, the nucleus proprius, and the neck of dorsal horn on the ipsilateral side of the spinal cord were counted. **Results**: Both of intracisternal morphine and intradermal compound 48/80 induced scratching behavior. The total number of Fos-LI cells significantly increased in C48 group (p=0.003) and M group (p=0.043), compared with respective control groups. A significant increase in the number of Fos-LI cells was found in the superficial laminae in C48 group (p=0.0072), but not in M group (p=0.707). **Conclusions**: Our data suggest that neurons in the superficial laminae play a more important role in peripheral than central itch.

PB11 ANTIPRURITIC EFFECT OF DEXMEDETOMIDINE OR CLONIDINE IS MEDIATED BY SPINAL α_{2A}-ADRENOCEPTORS

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Introduction: We previously reported that α_2- adrenoceptor agonists produced antipruritic action in mice. However, the site of action and α_2-adrenoceptor subtypes involved in the antipruritic effect of α_2-adrenoceptor agonists remain to be known. We conducted the present study to determine whether spinal or supraspinal α_2-adrenoceptors are responsible for the antipruritic effect of dexmedetomidine (DEX) and Clonidine (CLO), an α_2-adrenoceptor agonist, and which subtype of α_2-adrenoceptors primarily mediates this antipruritic effect in a mouse pruritoceptive itch model. **Methods:** Mice received intraperitoneal (i.p.) injection of DEX (0.3 µg/0.1ml) or CLO (1.0 µg/0.1ml), at 30 min after intracerebroventricular (i.c.v.) or intrathecal (i.t.) injection of yohimbine (Yoh; α_2-receptors antagonist, 10 µg/5 µl), BRL44408 (BRL; α_{2A}subtype preferring antagonist, 0.02 µg/5 µl), ARC239 (ARC; α_{2B}subtype preferring antagonist; 10 µg/5 µl), Rauwolscine (Rau; α_{2C}subtype preferring antagonist; 10 µg/5 µl) or vehicle (Veh; saline 5 µl). Animals that took abnormal postures continually after i.c.v. or i.t. injection were excluded. Immediately after i.p. DEX or CLO, mice received intradermal injection of compound 48/80 (100 µg/50 µl) on the rostral part of the back, and then the scratching behavior was recorded for 60 min using a video camera under unmanned conditions. Each recording was played back to count scratches at a site of body by a hind paw. Mice receiving i.c.v. or i.t. vehicle, i.p. vehicle, and intradermal pruritogen served as negative control. **Results:** DEX or CLO significantly decreased the number of scratches. The antipruritic effect of was prevented by i.t. yohimbine and i.t. BRL, but not by i.t. ARC, i.t. Rau, i.c.v. yohimbine, i.c.v. BRL, i.c.v. ARC, or i.c.v. Rau. **Conclusions:** Our data clearly indicate that in a mouse pruritoceptive itch model, systemic DEX or CLO produces a significant antipruritic effect primarily by activating α_{2A}adrenoceptors in the spinal cord.

PB12 COWHAGE SPICULES VIGOROUSLY ACTIVATE A SUBPOPULATION OF AD NOCICEPTORS IN MONKEY

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Intradermal insertion of cowhage (*Mucuna pruriens*) spicules produces the sensation of itch through a non histaminergic mechanism. Psychophysical studies in human suggest that small myelinated nerve fibers may contribute to the itch sensation, but little is known about the responsiveness of Aδ-fibers to pruritic stimuli. Therefore, we investigated in the anesthetized monkey the responses of small myelinated mechanically sensitive (MSA, n=43) and mechanically insensitive (MIA, n=16) afferents to cowhage, histamine and capsaicin. Inactive (i.e., non-pruritic) and active cowhage spicules were applied to the receptive field, followed by intradermal injections (volume 10 µl) of saline, histamine (10 µg), vehicle and capsaicin (10 µg). Responders were defined as afferents with at least 10 action potentials (APs) in the 5 min following stimulus application and with a total number of APs at least twice that of the control stimulus. All MSAs responded during application of the inactivated spicules, but activity was weak or non-existent thereafter (median: 0 APs/5min: quartile range: 0–2 APs/5 min). In contrast, active cowhage spicules elicited a vigorous response in 16 A-MSA fibers (median: 251 APs/5 min; range: 113–538 APs/5 min). Histamine evoked a much smaller response in 11 MSAs (median 42 APs/5 min; range: 16–94 APs/5 min) (p<0.001). Only 4 MSAs responded to both histamine and cowhage, and another 4 MSAs responded to capsaicin. Three additional MSAs were responsive to cowhage but not tested further. All 14 A- MIAs were unresponsive to cowhage; 2 MIAs were histamine responsive and 4 responded only to capsaicin. These results show that cowhage vigorously activates a sub-population of cutaneous A-MSA fibers, whereas A-MSAs only weakly respond to histamine. A-MIAs are not activated by cowhage. Neuronal activity in a subpopulation of mechanosensitive A- fiber nociceptors may contribute to itch sensation induced by cowhage.

PB13 HISTAMINE-INDUCED ITCH DOES NOT DEPEND ON THE ACTIVATION OF POLYMODAL NOCICEPTORS

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Activation of a specialized class of mechano-insensitive nociceptors has been claimed to underlie histamine-induced itch. However, recent results in monkey have suggested that also mechanosensitive polymodal nociceptors can provoke histamine induced itch. In order to allow differential stimulation of polymodal and mechano-insensitive nociceptors we performed a peripheral nerve block (Mepivacain 1%, 1ml) of the lateral femoral cutaneous nerve in 10 healthy volunteers and mapped the areas anesthetized for brush, pin-prick (100 and 260 mN), heat (45°C) and electrical stimulation (5mA at 1Hz). The nerve block induced larger anesthetic areas to mechanical (100 mN pin-prick: 402±61 cm^2; 260 mN pin prick: 374±57 cm^2, brush: 393±63 cm^2) and heat pain stimuli (401±53 cm^2) when compared to the fields identified for electrical sensitivity (352±62 cm^2). In one subject, no differential borders were identified for electrical and pin prick stimuli. Histamine was applied by iontophoresis (7.5 mC) at skin sites in which mechanical sensation was blocked, but electrical stimulation was still perceived 30 min after the nerve block (n=9). In these areas insensitive to mechanical stimulation, histamine iontophoresis provoked itching in 8/9 subjects with a mean maximum of 4.6±1 (numeric 11 point rating scale). We conclude that histamine induced itch can be perceived from skin sites in which input from mechano-sensitive polymodal nociceptors is blocked. Thus, the input from mechano-insensitive nociceptors is sufficient to generate histamine induced itch. Larger innervation territories of mechano-insensitive nociceptors are suggested to cause the differential sensitivity.

PB14 IMMUNOHISTOCHEMICAL LOCALIZATION AND EXPRESSION LEVELS OF TRANSIENT RECEPTOR ION CHANNELS (TRP) IN HUMAN SKIN AND PATIENTS WITH PRURITIC DISEASES

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Background: The transient receptor potential (TRP) superfamily of receptor proteins are known to be involved in a wide variety of neural sensation and are stimulated by both exogenous factors including temperature, spicy food, ethanol, mechanosensation, and toxins and by endogenous factors like pH changes and metabolites. Several members of the TRP family are expressed in sensory neurons and in both neuronal and non-neuronal cells of the epidermis and dermis. To this end, the physiological and pathophysiological role of these proteins in non-neuronal cells in the skin is uncertain. We hypothesize that several members of the TRP protein family may be involved in mediating itch sensation in pruritic skin disease, and therefore wish to investigate the distribution of TRP channels in normal skin and pruritic skin diseases. **Methods:** Punch biopsy samples from patients with pruritic skin disease were obtained and diagnoses were confirmed by clinical examination and histopathological review. We performed gene array studies and RT-PCR to determine gene expression levels of the TRP channels in human inflammatory skin disease. Additionally, paraffin sections were studied using immunohistochemistry with antibodies against TRVA1, V1, V2, V3 and V4. The results were quantified by morphometry. **Results and Conclusions:** Our results indicate that expression levels for many TRP protein family members differ in human inflammatory or pruritic skin disease when compared to normal human skin. Immunohistochemical staining and subsequent morphometric analysis demonstrates that TRP channels are expressed by various cutaneous cells as well as unmyelinated nerve fibers, and this differs amongst diseases. We hypothesize that TRP channels play an essential role in mediating the symptom of pruritus in various skin diseases and thus TRP family proteins may be good targets for itch therapy.

PB15 ROLE OF CAV1.2 L-TYPE CALCIUM CHANNEL IN XENOBIOTIC METAL INDUCED MAST CELL ACTIVATION

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Xenobiotic heavy metal ions including mercury, gold and silver ions have been shown to highly induce allergy including contact dermatitis and autoimmunity in genetically susceptible humans and/or experimental animals. Mast cells are implicated to play a role in the development of these immunological reactions. Recently, we reported that mast cells express $Ca_v1.2$ L-type calcium channel (LTCC), which regulates mast cell effector responses in a distinct manner from calcium release-activated calcium (CRAC) channels. Here, we report that Cav1.2 LTCC mediates xenobiotic metal-induced mast cell activation. Au (III) at concentrations up to 50 μM dose-dependently induced degranulation and leukotriene C_4(LTC_4) secretion without affecting cell viability. Au (III) also induced calcium influx and production of intracellular and extracellular H_2O_2, and scavenging H_2O_2, by the glutathione peroxidase mimetic ebselen blocked the calcium influx, degranulation, and LTC_4) secretion. The Au (III)-activated calcium influx was distinct from CRAC channels in terms of their sensitivities to pharmacological calcium channel blockers and calcium store emptying. Moreover, siRNA knockdown of $Ca_v1.2$LTCC completely abolished the Au (III)-activated calcium influx. Essentially similar results were observed with Hg (II). These findings may explain the fact that xenobiotic heavy metal ions induce autoimmunity by at least in part overlapping mechanisms.

PB16 EPIDERMAL NERVE DENSITY IS MODULATED BY KERATINOCYTES-PRODUCED ANOSMIN-1

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Epidermal nerve densities are increased in the skin lesions of atopic dermatitis (AD), suggesting that is partly involved in

abnormal itch perception. The innervation is probably controlled by axonal guidance molecules such as nerve growth factor and semaphorin 3A produced from keratinocytes. KAL1, encoding the extracellular glycoprotein anosmin-1, is responsible for the X chromosome-linked Kallmann syndrome. This protein has chemoattractive and chemorepulsive effects on different neuronal types. However, the roles of anosmin-1 in inflammatory skin diseases such as AD are poorly understood. Here, we report the effect of anosmin-1 on rat dorsal root ganglion (DRG), the expression of KAL1 at mRNA and protein levels in normal and atopic skins in humans, and the effect of cytokines involved in inflammatory skin diseases on its gene expression using cultured normal human epidermal keratinocytes (NHEK). In comparison with control cells, the neurite outgrowth in cultured DRG neurons was suppressed by conditioned medium from conditioned medium from KAL1 overexpressing CHO cells. In reverse transcription-polymerase chain reaction (RT-PCR) analyses, KAL1 was expressed in the cultured NHEK and the normal skin. Immunohistochemical analyses showed that anosmin-1 was strongly expressed in the epidemis of normal skin, especially in the basal cell layer but expression was decreased in basal cell layer in epidermis of AD patients. KAL1 expression was also downregulated during keratinocyte differentiation in vitro. Moreover, the gene expression in the cultured NHEK was upregulated by interleukine-4 (IL-4), IL-13 or TGF-β1. In combination with IL-13, TGF-β1 worked synergistically to enhance the KAL1 expression, while IFN-γ inhibited its expression. These results suggest the downregulation of anosmin-1 in inflammatory skin disease such as AD might be promote the penetration of nerve fibres into the epidermis.

PB17 DECREASED EXPRESSION OF SEMAPHORIN 3A IN THE LESIONAL SKIN OF PSORIASIS WITH ITCH

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It is known that an increase of epidermal nerve fibers is partly responsible for the itch sensations in skin disorders. Semaphorin 3A (Sema3A), which is a diffusible molecule important in repulsive axon guidance during neural development, may be involved in the modulation of epidermal innervation in skin disorders with itch. This study was performed to investigate a potential contribution of Sema3A to the modulation of epidermal innervation in psoriasis. Skin biopsies from normal skin of 30 healthy volunteers and lesional skin of 30 patients with psoriasis were used in this study. The mean value of visual analogue scale score was 45 in the patients with psoriasis. The expression pattern of Sema3A was examined immunohistochemically in the epidermis. For positive control of sema3A immunoreactivity, Sema3A knockout mouse and human brain were used. The protein was localized in the intercellular spaces between keratinocytes of hetero knockout mouse and in the intercellular spaces or cytoplasma of nerve cells. In contrast, immunoreactivity was not detected in the homo knockout mouse. In healthy volunteers, Sema3A was localized in the intercellular spaces between epidermal keratinocytes. The protein was remarkably decreased in the epidermis of psoriasis compared with that in normal skin. A significant decrease of Sema3A at the mRNA level in the skin of patients with psoriasis was also confirmed by quantitative reverse transcription polymerase chain reaction analysis. While the nerve fibers were occasionally present in the normal epidermis, they were observed at higher densities in psoriasis by nerve staining. We found that epidermal Sema3A levels were decreased in psoriasis compared with normal skin, concomitant with the increase of epidermal nerve densities. Our findings raise the possibility that the decreased expression of Sema3A accelerates the epidermal nerve growth in psoriasis with itch.

PB18 CATHEPSIN S IS AN ENDOGENOUS CYSTEINE PROTEASE, ELICITS ITCH, AND SIGNALS VIA PROTEASE-ACTIVATED RECEPTORS

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The sensation of itch is mediated by two distinct non-overlapping populations of cutaneous nerve fibers that evoke comparable degrees of itch. One set of fibers, the mechano-insensitive population, is more responsive to histamine than to cowhage. The other set is mechanosensitive and is more responsive to cowhage than to histamine. Histamine itch is associated with a wheal and flare. Since most clinical itches do not have a wheal or flare and do not respond to antihistamines, histamine is not thought to contribute to most itches. The active component of cowhage is mucunain, a cysteine protease that serves as a ligand for protease-activated receptors (PARs) 2 and 4. The identification of an endogenous mediator with properties similar to cowhage could lead to insights into non-histamine mediated itch. We focused on human cathepsin S because it shares active site sequence homology with mucunain and is selectively up-regulated in human keratinocytes upon stimulation with interferon-gamma, consistent with a possible pruritic role in inflammatory skin disease. Cathepsin S is a cysteine protease linked to inflammatory processes including atherosclerosis and asthma. The possibility that this or other cysteine proteases might evoke itch or be part of a classical ligand-receptor signaling cascade has not been considered previously. We show that human cathepsin S evokes itch and nociceptive sensations similar to mucunain and is a ligand for protease-activated receptors 2 and 4. Cathepsin S may be an endogenous activator of PARs and thus be a therapeutic target for the treatment of pruritus.

PB19 ACIDIC PH INDUCES MATRIX METALLOPROTEINASE (MMP)-9 (GELATINASE B) EXPRESSION AND CASPASE-3/7 ACTIVITY FROM KERATINOCYTE IN CULTURE

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Objective: Gelatinase expression in the epidermis to involve neurite outgrowth, which leads to pruritic lesion, is shown as a part of hypothetical mechanism on neuritogenesis of atopic NC/Nga mice by Tominaga and Takamori et al. Although the stratum corneum is reported to be kept acidic in comparison with inner layers of undifferentiated keratinocytes, stimuli from environment including scratch because of pruritus are considered to disturb this homeostasis of pH, which could cause the exposure

of acidic pH to inner layers of keratinocytes in the epidermis. MMP-9 (gelatinase b) and caspases have been shown to play important roles on a variety of occasions of cutaneous tissue metabolism including inflammation. Our recent study elucidated the mechanism of MMP-9 transcription enhanced by caspase-3/7 activity. In this study, the effect of acidic, low pH on the expressions of these enzymatic activities from keratinocyte in culture was investigated. **Methods:** Human primary keratinocyte under undifferentiated condition was cultured in low pH or not. Gelatinase activities from conditioned culture media and caspase-3/7, -8, or -9 activity from cell lysates were analyzed using gelatin-zymography and the cleavage activity of synthetic substrate for each caspase, respectively. **Results:** Low pH induced MMP-9 expression together with caspase-3/7 activity from keratinocyte. **Conclusions:** These results indicate that the induced activities of MMP-9 and caspase-3/7 in the epidermis caused by the exposure of acidic, low pH to undifferentiated keratinocyte by stimuli such as scratch because of pruritus itself could contribute to the neurite growth with the further pruritus.

PB20 THE BASIS OF TOPICAL SUPEROXIDE DISMUTASE ANTIPRURITIC ACTIVITY

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In humans, as in all mammals, three forms of superoxide dismutase (SOD) are present: SOD1 is located in the cytoplasm, SOD2 in the mitochondria, and SOD3 is extracellular. SOD is used in cosmetic products to reduce free radical damage to the skin, for example, to reduce fibrosis following radiation for breast cancer. Pruritus is one of the most common symptoms of skin diseases, but can also be a major symptom of systemic diseases (e.g., malignancy, infection or metabolic disorders). There are various antihistaminics used as antipruritogenic substances. In the genesis of pruritus there are many pruritogens involved, not only histamine and leukotrienes such as acetylcholine, cytokines, kallikreins, proteases, kinins, opioids, etc., which are described. On many occasions, we observed that topical SOD seemed to possess strong antipruritic activity, even in anti-histamine resistant pruritus. We analyzed literature data on the possible explanations of the effect of SOD as an anti-pruritogen on NK-1 receptors and proinflammatory cytokines, its regulatory role in calcitonin gene-related peptide production and expression, down-regulation of TNF-α and numerous cytokines, and suppression of nitric oxide production.

PB21 IDENTIFICATION OF LYSOPHOSPHATIDIC ACID AS NEURAL ACTIVATOR IN BLOOD OF PRURITIC CHOLESTATIC PATIENTS

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Pruritus is a burdensome symptom of various, mainly cholestatic hepatobiliary diseases. The pathogenesis of pruritus in cholestasis is still poorly understood. Bile salts and opioids have, among others, been implicated in the aetiology of pruritus, but a relation with itch intensity could never be established. **Purpose:** We hypothesized that potential pruritogens accumulate in the circulation of cholestatic patients and activate neurons by (in) direct stimulation. To identify potential pruritogens we screened sera of pruritic cholestatic patients for activation of different neuronal cell lines. **Methods:** Cytosolic free calcium $(Ca^{++})_i$ was measured in neuronal cell lines by ratiometric fluorimetry upon exposure to diluted serum samples of patients with intrahepatic cholestasis of pregnancy (ICP; *n*=31), pregnant controls (PC; *n*=29), patients with other causes of cholestasis (mainly primary biliary cirrhosis; *n*=30) and healthy subjects (HC; *n*=30). The $(Ca^{++})_i$ inducing factor in pruritic sera was identified by various analytical techniques including protease treatment, lipid extraction, reverse-phase column binding, influence of pH changes, size analyses, receptor blockage, and quantification by HPLC-MS. In mice scratch activity after intradermal pruritogen injection was quantified using a magnetic device. **Results:** Transients in $(Ca^{++})_i$ in human SH-SY5Y neuroblastoma cells, induced by sera from pruritic ICP and PBC patients were significantly higher than those of corresponding controls. On the basis of physicochemical properties, lysophosphatidic acid (LPA) could be identified as major $(Ca^{++})_i$ agonist in pruritic sera. Indeed, serum LPA concentrations were significantly increased only in those cholestatic patients that suffered from pruritus. LPA injected intradermally into mice (22 nmol) induced scratch responses. **Conclusion:** Our data suggest that LPA plays a key role in cholestatic pruritus. We speculate that LPA receptor blockers may be useful as antipruritic agents in treatment of cholestatic pruritus.

PC01 ASSESSMENT OF PRURITUS INTENSITY: CORRELATION BETWEEN VISUAL ANALOGUE SCALE, NUMERIC RATING SCALE AND VERBAL RATING SCALE IN PATIENTS WITH CHRONIC PRURITUS

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The most commonly used tool for self-report of itch intensity is the visual analogue scale (VAS). Similar measurement tools are the numeric rating scale (NRS) and verbal rating scale (VRS). We herein present data of the first study in which reliability and concurrent validity of VAS, NRS and VRS in chronic pruritus were investigated. 84 patients (39 m, 45 f, mean 60.71 years) recorded their pruritus by VAS (10 cm line), NRS (0–10) and a four-point VRS scale. 11 patients stated no itching on VAS=0 (mean point difference [MPD] to NRS 0.64), 46 patients rated itching as low on VAS (0.1–3.9, mean 1.50; MPD 0.85), 12 patients as moderate on VAS (4.0–7.9, mean 5.87; MPD 1.01) and 8 patients as severe pruritus on VAS (8.0–10, mean 9.16; MPD 0.39). On the VRS, 6 patients stated to have no itch ("0") which was scored in mean as 0.08 (VAS) and 0.0 (NRS). 40 patients stated to have low ("1") pruritus (mean VAS/mean NRS: 1.22/2.00), 26 patients to have moderate ("2") pruritus (mean VAS/mean NRS: 3.72/4.46) and 9 patients to have severe ("3") pruritus (mean VAS/mean NRS: 9.02/9.00). 7 patients did not record their pruritus intensity by VAS, 2 patients not by NRS and 3 not by VRS. The correlation coefficient for VAS with NRS was 0.947, for VAS with VRS 0.826 and for NRS with VRS 0.863. In sum, VAS, NRS and VRS showed a high reliability

and concurrent validity, especially VAS and NRS with a low point difference of mean 0.79, SD 0.87. Thus, all can be used in clinical trials to assess valid data of itch intensity course. The NRS and VRS are easier to understand and handle for patients; however, for the discrimination of itch intensity the VRS is not as sensitive as VAS and NRS.

PC02 HOW TO MEASURE ITCH INTENSITY? A SYSTEMATIC LITERATURE REVIEW

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Aims: Giving an overview on development of and research on itch intensity measurements reported in literature. **Methods:** A systematic literature review was performed using the medical database PubMed. Search topics were 'pruritus', 'itch', 'itching', 'measurement', 'measuring', 'outcomes', and 'visual analog(ue) scale' in appropriate combinations. Results were reviewed for itch measurement methods and data on test criteria. Furthermore, article references and books on pruritus were reviewed. Because of the related perception to be measured, a literature search on pain measurement was performed in addition. **Results:** A wide range of measurements of itch intensity has been developed so far. They can be classified as (1) measurements of correlates of itch intensity and (2) patient judgement of itch intensity. Regarding both itch and pain intensity, patient judgement measurements can be divided into (a) visual analogue scales, (b) numerical rating scales, (c) verbal rating scales, and (d) composite scales. Scales differ regarding verbal description, usage of smileys, scale graduation, orientation, device used, and time period rated. Validation studies on intensity measurements have been conducted mostly in pain rating, but only few in itch rating; results are mixed. Moreover, validity was mainly assessed regarding the criterion of short-term changes in pain. **Discussion:** Although many different itch intensity measurements have been developed, rather little is known about reliability and validity of these measures. Especially regarding the measurement of changes in itch intensity over a longer period, which is essential in itch treatment evaluation, development and validation of feasible and robust scales are needed.

PC03 PATIENTS WITH CHRONIC PRURITUS TREATED IN A SPECIALIZED ITCH CLINIC: RESULTS AND EXPERIENCES

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Pruritus is the most frequent and distressing symptom in many dermatoses and various e.g. internal, neurological and psychosomatic diseases. 211 patients (102 men, 109 women, mean age 58.8 years) suffering from chronic pruritus (defined as lasting longer than 6 weeks) consulted the itch clinic of the University Hospital of Heidelberg, Germany. To make manifestation and aetiology of the pruritus comparable, all patients were classified according to the International Forum for the Study of Itch (IFSI) classification and according to the manifestation of skin lesions. Data analysis focused on disease history, occurrence of concomitant diseases, present and past therapy, quality, frequency and triggers of itching and scratching, and quality of life. 71.7% of the patients had a history of pruritus lasting one year or longer. 13.0% had been suffering from chronic pruritus for a minimum of 10 years. 29.9% of the patients suffered from pruritus due to dermatoses, 20.4% due to a systemic disease and 6.2% due to a neurological disease. In 12.3% of chronic pruritus patients, it was classified as somatoform, 21.8% had mixed origins and in 9.5% of patients pruritus was of undetermined origin. None of the patients with neurological pruritus had generalized pruritus. 42.3% of the patients with somatoform pruritus reported it to be localized at the scalp or the genital region. Localized scalp or genital pruritus reveals a probability of 26.8% to be of somatoform origin. If the patient's skin was not primarily diseased or inflamed and pruritus was generalized, the probability of a systemic disease was 48.8%. 71.4% of the patients had a reduced quality of life, this was most frequent in the group of patients suffering from somatoform pruritus (85.7%). All patients who consulted the itch clinic are followed-up for identifying the course of chronic pruritus and evaluating the success of the introduced therapies.

PC04 ESTIMATING THE PREVALENCE OF CHRONIC ITCH: HOW COMMON IS THE SYMPTOM?

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Background: Epidemiological data on chronic pruritus, that is itch lasting for more than six weeks, is sparse but important in order to understand burden and risk factors of this distressing symptom. Given this sparsity of data, the Epidemiology of Chronic Pruritus Research Group (ECPRG) based at the University Hospital Heidelberg, Germany, set out to undertake a population based study on chronic pruritus. Here, we report on the prevalence of chronic pruritus. **Method:** Addresses of 4500 German citizens were obtained from the registers of local residents in two cities and 6 rural communities in Southwest Germany at random. A previously validated questionnaire was sent out by mail. A reminder was sent after 2 months to all non-responders. The remaining non-responders were contacted by telephone if their number was listed in the telephone directory; if the number could not be obtained a third reminder including a shortened version of the questionnaire was sent. **Results**: Of the 4500 individuals contacted 86 were ineligible to participate leaving a total sample of 4414. The total response rate was 59%. The point-prevalence of chronic pruritus was 14.7% (95% CI 13.3%–16.2%), the 12-months prevalence 17.4% (95% CI 15.9%–19.0%) and the lifetime prevalence 23.8% (95% CI 22.2%–25.6%). **Conclusion**: The results from this study suggest that burden of chronic pruritus in the general population is substantially higher than previously believed. One quarter of the population has suffered from chronic pruritus at least once in their life.

PC05 CHARACTERISTICS OF PRURITUS AMONG TURKISH PATIENTS ATTENDING A DERMATOLOGY CLINIC

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Background: Although pruritus is regarded as the hallmark symptom of dermatology, epidemiological data on its prevalence and clinical characteristics are far from adequate and most commonly limited to analyses of itch due to a specific cause such as

renal failure or atopic dermatitis. This study aimed to investigate the clinical presentation of pruritus at a dermatology outpatient setting. **Materials and method:** All patients seen at the dermatology outpatient clinic of a university hospital within a one year duration were questioned for the presence and severity of pruritus on a scale of 0 to 4 (no, mild, moderate or severe itch). Possible associations of pruritus frequency and intensity with various demographic parameters, itch localization and the preliminary dermatological diagnoses were analyzed using the SPSS 14.0 statistics program. **Results:** A total of 3937 patients, 2360 (59.9%) females and 1577 males (40.1%) of ages between 2-95 years (mean:38.6±18.9) were included. 40.0% complained of pruritus at the time of their examination. The itch was described as severe in 32.25%, moderate in 29.50% and mild in 38.25% of the pruritic patients. Presence of pruritus did not have a gender preference but a statistically significant association with increasing age was observed. Women complained of severe pruritus slightly more frequently than men (13.8 vs 11.5%). Patients with pruritus were more often seen in the beginning of the work week. Pruritus was most commonly generalized (32.2%). Genital pruritus led the list of areas with severe pruritus followed by feet. Although fungal diseases and eczema were the diagnoses most frequently associated with pruritus, the symptom was more often reported as severe in patients with urticaria and pruritus on nonlesional skin. **Conclusion:** Not only a very prevalent symptom, pruritus is an entity with complex associations deserving further epidemiologic research worldwide.

PC06 HIGH PREVALENCE OF PRURITUS ASSOCIATED WITH POOR OUTCOME IS STILL COMMON IN HEMODIALYSIS PATIENTS

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Background: Pruritus is a distressing symptom in many patients receiving chronic hemodialysis (HD). In the international Dialysis Outcomes and Practice Patterns Study (DOPPS) we previously reported that 45% and 42% (DOPPS I and II, respectively) of prevalent HD patients experienced moderate to extreme pruritus. The current follow-up study was undertaken to investigate whether changes in care of patients have influenced the prevalence of pruritus. **Methods:** The degree of pruritus was self-reported from 7151 HD patients in DOPPS III during 2005-2006. Logistic and Cox regression analyses were adjusted for age, gender, black race, spKt/V, haemoglobin, serum albumin, 13 comorbidities, depression, years on dialysis, and country, and accounted for facility clustering effects. Cox regression analyses were further adjusted for albumin-corrected serum calcium, serum phosphorus, and depression. **Results:** Moderate to extreme pruritus was experienced by 41% of prevalent HD patients. Many patient characteristics were significantly associated with pruritus, but this did not explain the large differences in pruritus between countries (ranging from 37% in Spain to 49% in UK) and between facilities (4 to 88%). Patients with moderate to extreme pruritus were more likely to feel drained (adjusted odds ratio, AOR=2.87, $p<0.001$) have poor sleep quality (AORs=1.24-2.17, all $p<0.001$), have a diagnosis of depression (AOR=1.40, $p<0.001$), and have QoL mental and physical component summary scores 3.77 and 3.27 points lower ($p<0.001$), respectively, than patients with no or mild pruritus. Moderate to extreme pruritus in HD patients was associated with a 11% higher mortality risk ($p=0.04$), which was reduced and no longer significant after further adjusting for sleep quality measures. **Conclusions:** The prevalence of pruritus and many associated poor outcomes continues to be common in HD patients despite changes in dialysis care.

PC07 COMPARISON BETWEEN PERCEIVED ITCH INDUCED BY SKIN PRICK-TESTS WITH HISTAMINE OR CODEINE

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The role of personal factors makes it difficult to correlate subjective data, such as those obtained with the use of a visual analogue scale, and objective data, such as a quantity of injected histamine. In this study, prick tests on forearms with histamine and codeine allowed to obtain a coherent variation of itch scores over time, with highly significant differences with controls and with a peak at 4 min. These tests appear valuable for screening of anti-pruritic agents. A significant difference between initial scores and scores after new prick tests after 7 days suggest that tachyphylaxis persists.

PC08 EVALUATION OF PSORIATIC ITCH BY EPIDERMAL NERVE DENSITY AND OPIOID RECEPTOR LEVELS

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Psoriasis is one of the common chronic inflammatory skin diseases. The patients with psoriasis show the erythematous plaques with or without itch. Previous studies have been reported that approximately two-thirds patients with psoriasis are associated with itch but intense itch (e.g. atopic dermatitis) is rarely found in the patients. Conventional treatment such as antihistamines often lack efficacy in psoriatic patients with itch. In the patients, itch also induces scratching, and brings about aggravation of exanthema by the kobner phenomenon. It is clinically important to control itch in patients with psoriasis, although the mechanisms of itch are poorly understand. Moreover, numerous factors (e.g. cytokines, neuropeptides) involving in the pathology of psoriasis are found but the correlation with itch is unclear. Our recent studies have shown that epidermal nerve density and expression levels of opioid systems are related in itch perception of patients with atopic dermatitis. In this study, we investigated the pathogenic mechanisms of itch of patients with psoriasis by examining nerve density, expressions of semaphorin 3A, mu- and kappa-opioid receptors in the skins of psoriatic patients with or without itch. Penetration of nerve fibers into the epidermis were observed in approximately 40% and increases of the papillary dermal nerves in psoriatic patients with itch. Epidermal semaphorin 3A levels also tended to decrease in the patients. These results suggest that the epidermal nerve densities are partly responsible for psoriatic itch and that other factors (e.g. opioids) might be involved in the pathogenic mechanisms of itch. In the workshop, we will report about the relationship between expression levels of opioid systems in the psoriatic skins and itch.

PC09 PRURITUS AND PSORIASIS: CLINICAL STUDY

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We studied clinical, sensitive and emotional characteristics of pruritus in psoriatic patients. The clinical form and severity (PASI) of psoriasis were defined. Clinical characteristics included: the duration of pruritus; cycle of itch during day/night; factors, aggravated or improved itch; itch influence for daily activity; pruritus and sleeping. We used visual analogue scale (VAS) from 1 to 10 for subjective assessment of intensity of itch. For sensitive and emotional study a questioneer was used. 31 patients with itch (20 men and 11 women) aged from 15 to 74 were enrolled to the study. The duration of the disease was 16.7±9.4, the duration of itch 4.6±5.4. Clinical forms: psoriasis vulgaris in 28.3% of patients, exudative in 30%, erythroderma in 41.7%. PASI was 7–66.6. In order to demonstrate the correlation between clinical form and itch 10 psoriatic patients (vulgaris and guttata forms) without itch were registered. VAS was 12.8±4 (moderate): 8±3.8 (mild) – in the group with vulgaris form, 13.3±4,4 (moderate) in exudative form, 15.5±3.5 (severe) in patients with erythroderma. The most of patients had gradual onset of pruritus, it began in several years after proriasis onset. 41% patients noted aggravation of the pruritus in night and 90.5% persons daily complaint of itch. The dryness, sweeting are the most common aggravating itch factors; hot bath, warm bath, scratching, moving are improving factors. The most severe pruritus is registered in patients with exudative psorisis and erythroderma. Patient with vulgaris may have slight or moderate itch. Psoriasis vulgaris and guttata may occur without itch. The positive correlation is revealed between clinical severity of psorisis and severity of itch (r=0.7). The most common sensitive characteristics are stabbing (61%), painful (51%), burning (48%); emotional & unpleasant (74%), bothersome (61%), annoying (51%). The most severe was emotional perception as quantities as qualitive.

PC10 PRURITUS AND WORK ABILITY IN PSORIATIC PATIENTS

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Objective: The aim of the study was to evaluate the influence of itching on the work ability in patients with psoriasis. **Materials and methods:** A total of 126 patients (68 females and 58 males) with psoriasis aged between 16 and 81 years (mean: 49.0±14.0 years) were included into this study. Severity of disease assessed according to PASI ranged between 0.1 and 28.5 points (mean 7.9±6.0 points). A specially designed questionnaire was completed for each patient based on the anamnesis. In addition, every participant fulfilled the Work Questionnaire (Work-Q) of Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). Itching intensity was measured by visual analogue scale (VAS). **Results:** Ninety three (73.8%) patients experienced pruritus during psoriasis exacerbation. A weak, but significant correlation was found between disease severity and pruritus intensity (R=0.23, p=0.01). About one third of patients (33.9%) claimed that psoriasis had small effect on their work activity, 44 (40.4%) declared moderate and 23 (21.1%) severe effect on the work ability. The rest 5 (4.6%) subjects stated that they could not work at all because of psoriasis. The most disturbing symptom of psoriasis during work was scaling (63.5%) followed by pruritus (48.4%) and nail crumbling (18.3%). Patient with more impaired work ability had higher pruritus scoring (3.2±3.0 vs. 4.2±2.9 vs. 4.9±2.7 vs. 6.2±2.3 points, p=0.05). A significant correlation was found between pruritus intensity and work activity (R=-0.31, p<0.01). Patients with pruritus had also lower scoring in Work-Q compared to patients without itching (69.6±16.6% vs. 77.7±16.2%, p=0.01). **Conclusions:** Pruritus may decrease the work ability in patients with psoriasis.

PC11 CLINICAL OBSERVATIONS ON GENERALIZED PRURITUS: A RETROSPECTIVE STUDY

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Although generalized pruritus without primary skin lesion is a relatively common condition which may persist for months to years, little study has been carried out. Therefore we attempted to determine the causes, clinical manifestations, treatments and courses of the generalized pruritus. Our study included a total of 229 new patients at Kyungpook National University Hospital, Daegu, Korea (190 newly visited dermatologic outpatient, 39 consulted inpatient from other clinical departments) with generalized pruritus without skin lesion from July 2005 to June 2008. Data was reviewed on the basis of a retrospective survey of hospital records. Additional phone calls to the patients were made by doctors. For the result, the number of the patients with generalized pruritus was highest in the seventh decade of age. In 57.2% of total patients, generalized pruritus was a symptom of the internal disease. Idiopathic pruritus was in 20.6%, and senile pruritus was in 14.8% of the patients. Among internal diseases, endocrine disease was the most common (29.0%). Temperature change was the most frequent (20.3%) aggravating factor. For diurnal and seasonal variations, pruritus was frequently aggravated at night (36.0%) and in summer (18.8%). An approach to the workup of a patient with generalized pruritus is suggested in this study.

PC12 QUALITY OF LIFE IN CHRONIC PRURITUS MEASURED WITH ITCHYQoL

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Chronic pruritus has been shown to affect patients' quality of life (QOL) and we now seek to understand the impact of itch on QOL using the previously validated, condition-specific measure, ItchyQoL. We collected demographic information, asked general itch questions, and administered ItchyQoL, which contains questions about symptoms, functional impairment, and emotional distress, with each item scored from one to five, where higher scores represent more QOL impact. Patients who were itchy for over 6 weeks were recruited from the Atlanta Veterans Administration Medical Center Dermatology Clinic. We recruited 96 patients and found that 75% itched most or all the time; 56% itched for greater than 5 years. Self-reported severity on a 10-point scale was dichotomized into mild/moderate (1–6) and severe (7–10). Activities of daily living (ADL) were impaired in 61% due to itch severity: 74% with severe itch indicated ADL impairment versus only 48%

with mild/moderate itch (p=0.0085). The severe itch group showed significantly greater (p<0.05) involvement of the chest/abdomen and genitals/buttocks. While >20% of patients were able to identify a systemic or medication-related etiology, there was no difference between the severe and mild/moderate groups. ItchyQoL revealed a significant difference in mean overall QoL impact between the severe (3.17±0.94) and the mild/moderate (2.19±0.068) groups (p=0.0067). There was also a significant difference between the two groups in the subscales of symptom (3.34 vs. 2.36, p=0.001), functional impact (2.36 vs. 3.13, p=0.03) and emotion (2.04 vs. 3.05, p=0.04). This study is limited by the relatively small, specific population which may affect the generalizability of results, but demonstrates the that the burden of pruritus as measured by the sensitive ItchyQoL correlates to itch severity and may be related to anatomical area. Future work involves multivariate analyses to elucidate predictors of QoL impact.

PC13 THE ROLE OF TARC AND ITCH IN PATIENTS WITH ATOPIC DERMATITIS

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Thymus and activation regulated chemokine/CCL17 is a chemokine that attracts and activates Th2-type T cells. We have examined the serum concentration of TARC, CTACK, SCORAD and itch VAS score before and after the treatment of oral administration of cetirizine hydrochloride (10mg per day) and topical corticosteroid in patients with atopic dermatitis for 4 weeks (n=6). The average SCORAD changed from 34.1 to 19.5 before and after the treatment. The average serum TARC levels decreased from 1251.7 to 832.5 pg/ml, and serum CTACK levels decreased from 1430.9 to 1022.1 pg/ml, respectively. The average icth VAS score changed from 5.6 to 2.7 .Our results indicate that oral administration of cetirizine decreases serum TARC and CTACK levels resulting in the improvement of the eruption as well as itch. Our data suggest that cetirizine hydrochloride decreases the itch VAS levels through regulating TARC and CTACK production in atopic dermatitis.

PC14 TARGETING THE NEUROKININ RECEPTOR 1 AS A NEW ANTIPRURITIC STRATEGY: RESULTS OF A CASE SERIES WITH APREPITANT

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Treatment of chronic pruritus is still a challenge and development of new therapeutic strategies for these up to date insufficiently treated patients is mandatory. Due to the major role of Substance P in induction of cutaneous pruritus we applied the neurokinin receptor 1 (NKR1) − antagonist aprepitant in a case series of patients. 20 patients (12 female, 8 male; mean age, 66.7 years) with chronic pruritus (mean duration, 61.3 months) were treated. Aprepitant 80 mg was applied for 3 to 13 days (mean, 6.6) once daily. Itch intensity was recorded daily on the Visual Analog Scale (VAS) ranging from 0 (no pruritus) to 10 (severe pruritus). 16/20 patients (80%) responded to aprepitant. Mean value of VAS was reduced from 8.4 points (SD±1.7) before treatment (VASpre) to 4.9 points (SD±3.2; p< 0.001; CI 1.913−5.187) after treatment (VASpost). Patients with atopic predisposition and prurigo nodularis responded best to the treatment with a mean pruritus reduction of 54% (VASpre 8.2; SD±1.8; VASpost 3.8; SD±2.8; p= 0.001; CI 2.144−6.656) and 48.5% (VASpre 8.4; SD±1.8; VASpost 4.4; SD±3.2; p= 0.001; CI 1.863−6.137). Side-effects were observed in 3/20 patients. Side-effects were observed in 3/20 patients and comprised nausea, vertigo, and drowsiness. These findings support the important role of SP as mediator of chronic pruritus and for the first time provide evidence that targeting NKR1 − the major receptor for SP − is a highly effective treatment of chronic pruritus. Future controlled trials will have to prove the efficacy and safety of this novel strategy.

PC15 ANTIPRURITIC POTENCY OF THE TRITERPENE BETULIN IN PATIENTS WITH CHRONIC PRURITUS

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Betulin is the lead substance of a group of pentacyclic triterpenes which can be found in particular in high concentrations in the cork of the white birch (betula alba). Experimental studies suggested that triterpenes induce cutaneous anti-inflammatory effects and wound healing. An open-labelled trial aimed to investigate the antipruritic effects in 64 patients with chronic pruritus on inflammatory skin (group 1: n=20, 10 female, 10 male; mean age 55.5 years), pruritus on unchanged skin (group 2: n=23, 10 female, 13 male; mean age 57.4 years) and with chronic scratch lesions (group 3: n=21, 13 female, 8 male, mean age 62.0 years). A Betulin containing cream was applied for a period of two weeks twice daily on the affected areas followed by two weeks without cream and a follow-up visit. Before and after therapy, patients received a detailed clinical investigation with documentation of present scratch lesions assessed by the prurigo-score. For daily documentation of pruritus intensity patients used the visual analogue scale (VAS) from 0 to 10. Statistical analysis was done by intention-to-treat analysis. An antipruritic effect was documented in 50% of group 1 (10/20), 39.1% of group 2 (9/23) and 57.1% of group 3 (12/21). The mean reduction of pruritus intensity (in percent) was 49.3% in group 1, 66.9% in group 2 and 65.3% in group 3. Patients of group 3 showed a significant regression of scratch lesions within two weeks of cream application (mean prurigo score before/after therapy: 2.73/2.04; p=0.012). Most of the patients (90.6%) tolerated the therapy well. Six patients discontinued cream application before the second week. The present results suggest that the topical use of betulin is an effective antipruritic treatment option with good compatibility in patients with chronic pruritus, especially in patients with chronic scratch lesions.

PC16 SUCCESSFUL TREATMENT OF THERAPY RESISTANT PRURITUS IN LICHEN AMYLOIDOSIS WITH MENTHOL

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Lichen amyloidosis is a chronic pruritic skin disease characterised by brownish-grey papules on the extensor surfaces of

the legs and rarely on the trunk. A variety of therapeutical regimes for lichen amyloidosis has been described, in many cases only with limited effect. We report about a 67-year old woman suffering from severe pruritus (VAS 8–9) due to lichen amyloidosis on the back for more than 26 years not responding to various local and systemic treatments. Topical therapy with menthol 2 % cream (oil-in-water emulsion) twice daily was initiated resulting in nearly complete resolution of the papules and impressive relief of pruritus within 3 weeks (VAS 2). The beneficial response has been persisting for 18 months. The patient continues topical menthol therapy intermittently up to now. She describes it as the best therapy she has ever received. The way of antipruritic action in our patient is not clear but the following aspects may be considered: Menthol's ability to chemically trigger the cold-sensitive TRPM8 receptors in the skin is responsible for the well known cooling sensation that it provokes when inhaled, eaten or applied to the skin. Menthol was shown to disperse through the stratum corneum, disrupte the regular organisation of these structures and increase drug partition and diffusion parameters. The transient increase of transepidermal water loss (TEWL) suggests a possible role as a percutaneous penetration enhancer e.g. for urea used in topicals. Menthol has been shown to selectively activate κ-opioid receptors possibly explaining its antipruritic properties. This case report demonstrates for the first time that topical menthol therapy can be an effective and practical treatment for lichen amyloidosis with long-lasting effects.

PC17 FUNCTIONAL ITCH AND MENTAL DISORDERS IN DERMATOLOGICAL CLINIC (RESULTS OF PILOT STUDY)

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Background: Pruritus or itch is considered as a complex phenomenon observed in 35% of dermatological outpatients and in 33% of psychiatric patients. Thus mental disorders are not just a result of pruritus. There is a high comorbidity of itch and psychiatric disorders when pruritus is an equivalent to other psychopathological symptoms. In the cases it is difficult to find any dermatological/somatic cause of itch (functional itch). **Objective** of the study is to analyze interrelations of functional pruritus and mental disorders in a dermatological clinic. **Methods:** Clinical and psychopathological observation of 20 patients (8 male, 12 female; mean age 48.8±19.4 years) with medically unexplained itch consulted in the Department of dermatology of I.M.Sechenov Moscow Medical Academy. **Results:** Two types of pruritus were distinguished: episodic (1.5–2 months, *n*=3) and chronic (4.1±3.2 years, *n*=17). Episodic pruritus developed during depressive and pseudosomatic episodes. Itch correlated with severity and duration of mental disorders and reduced along with their improvement. Chronic pruritus was associated with undifferentiated somatoform disorder (*n*=15) and paranoiac psychosis with hypochondriac delusions (*n*=2). In undifferentiated somatoform disorder itch was accompanied with other medically unexplained complains and corresponding neurotic ideation. Self-destructions included scratch resulted in single excoriations and crusts. In paranoiac psychosis with hypochondriac delusions functional pruritus was accompanied by delusional and severe autodestructive behavior. Delusions were limited to assurance in undiagnosed skin disease presenting with itch and "lesions" (artificial in examination). Autodestructions involved not only scratch, but also use of tools (needle, scalpel), that resulted in identification of "underpasses" in the skin between lesions or fragments of "foreign tissue". Patients argued doctors to prove "yet undiscovered" skin disease denying any possibility of a psychiatric disorder. **Conclusion:** Functional pruritus is a heterogeneous clinical phenomenon associated with different mental disorders of various severity.

AQUAGENIC PRURITUS IN POLYCYTHEMIA RUBRA VERA PATIENTS – AN OBSERVATION OF 2 CASES OVER A PERIOD OF 2 YEARS *PC18*

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About half of PV patients suffer from severe pruritus, 10% of them suffering at the onset of the disease. The typical sensation is a burning and pricking itch after bathing or after taking a shower. AP impairs the quality of life of PV patients to a very high degree. The role of histamine in the pathogenesis of AP has always been controversial: serum histamine levels had been found to increase after having had a shower, however the therapeutic response of AP to antihistaminic drugs was always poor. Two patients were observed – a 67-year-old man and a 73-year-old woman, who had both suffered from PV for several years before the first dermatological consultation. There was no relationship between the symptoms and the time of day, season, mealtime or therapeutic procedures like blood-letting. The intensity of AP was measured continuously by a visual analogue scale from 1 to 10. A V617F point mutation in the Janus-Kinase-2 gene was detected in both patients. Skin biopsies were taken from the backs of both patients before and after any contact with water. The histological diagnosis in both cases was normal skin; no alteration of the nerve growth factor (NGF) could be seen. Over a period of more than two years the two patients underwent various therapeutical procedures. UVB irradiation, various ointments and lotions, medication with antihistamines like loratadine, cetiricine, clemastine and ebastine, acetylsalicylic acid, clopidogrel, antidepressive drugs like paroxetine, and pregabalin. Pregabalin proved to be the most effective drug against AP in the two PV patients. Pregabalin, traditionally a painkiller, is therefore the suggested drug of choice for the long-term treatment of PV patients.

DOUBLE DOSE OF CETIRIZINE IS EFFECTIVE FOR URTICARIA PATIENTS HYPO-RESPONSIVE TO THE ORDINARY DOSE *PC19*

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Objective: When an ordinary dose of antihistamine is insufficient in treating urticaria, an increased dose of the same drug or change of the drug is recommended. However, few reports have demonstrated evidence on this topic. We therefore evaluated the effect of double-dosing or changing drugs in patients who responded insufficiently to oral cetirizine at 10 mg/day. **Methods:** Fifty-one patients with urticaria (16 males and 35 females, aged 39.0±18.1 years) were enrolled and administered 10 mg of cetirizine once daily for an average of 10.1±7.3 days (period A). In

those who responded well to the treatment, the same dose was continued. Those who responded insufficiently to the initial dose were randomized to either twice-daily dosing with 5 mg of olopatadine (drug-change group) or once-daily dosing with 20 mg of cetirizine (dose-increase group), and treated for an average of 13.3±8.3 days (period B). The effect of both treatments was compared in terms of the severity of wheals and itching, and QoL scores based on a Japanese version of Skindex-16. **Results:** At the end of period A, a reduction in wheals was observed in 64.7% (33/51) of patients treated with 10 mg/day of cetirizine. Of the remaining 35.3% (18/51) of the patients who were less responsive to the initial dosage, 9 each were randomized to the drug-change or dose-increase groups. At the end of period B, significant reductions in the wheals and itching (nocturnal) were observed in the dose-increase group, but not in the drug-change group. However, all of the enrolled patients showed significant improvements in their global QOL score and in all scales (symptoms, emotions, and functioning). **Conclusion:** When the effect of cetirizine on uricaria is insufficient at an ordinary dose of 10 mg/day, doubling the dose to 20 mg/day is the next recommended step in treatment.

PC20 CAUSES OF CHRONIC PRURITUS: PATIENT PERCEPTIONS

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Patient's illness perceptions have a great influence on compliance and doctor-patient-relationship. A main component of the patient's perceptions is formed by the perceived causes of pruritus. For persons suffering from chronic pruritus, the symptom is a great burden. Causation, therefore, is of major importance for them, because – apart from successful treatment – it 'legitimates' pruritus in their social environment. We present results about the perceptions of causes in patients suffering from chronic pruritus. Data were obtained from half-guided interviews performed with sixteen chronic pruritus patients who differed in known or presumed underlying cause and localization of pruritus according to the classification of the International Forum for the Study of Itch (IFSI). Interviews were analyzed with content analysis. The patients' perceptions of causes of chronic pruritus differed vastly from the causes identified by medical examination. Almost all participants reported not to know the cause of pruritus. At the same time, they speculated about many different factors which may have induced the symptom. The factors were placed in personal and temporal context, like cumulated strain and interactions with medical treatment of other medical problems. Many interviewees recognized a psychic component, be it as a direct cause or as a triggering factor. Altogether, a complexity of perceived contributing factors causing chronic pruritus was identified. Patients who cannot accept the fact of ignoring the (medical) cause try several therapeutic possibilities and search extensively themselves to reveal the origin of pruritus. These findings underline the importance of open communication between MD and patient so they may learn the differing concepts of chronic pruritus from each other. This offers an opportunity for correcting misleading beliefs, finding a shared basis for effective treatment and for an adequate illness management.

PC21 STRESS MANAGEMENT ALLEVIATES ATOPIC PRURITUS

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Atopic dermatitis (AD) is a chronically pruritic skin inflammation. While the Th2-type immune responses contribute to AD pathogenesis, recent observations have provided evidence that psychological stress worsens AD symptoms. Itching not only bothers AD patients but also affects family's quality of life, strengthening the importance of itch regulation in AD treatment. We found that persistent anxiety shifts the immune responses to Th2-dominance in AD patients (Hashizume et al, BJD 2005). In this report we clarified the relationship between itching and anxiety in AD patients who had been hospitalized for AD educational program. In severe AD patients with SCORAD index ≥50, itching intensity was positively correlated to the trait anxiety/state anxiety ratio. Both coping mental stress with a sedative drug (Tandosprone) and the educational intervention ameliorated anxiety and reduced itching intensity in severe AD patients. Our observations suggest that the management of persistent mental stress is one important strategy to control pruritus in AD.

PC22 DEPRESSION-RELATED PRURITUS: A CLINICAL STUDY

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The problem of pruritus in psychiatric subjects has been underestimated for a long time, however, these individuals may suffer from itching, sometimes very severe one. Evaluation of prevalence and severity of itching in patients suffering from depression. A total of 64 subjects with depression were enrolled into the study. Their age ranged between 21 and 78 years. The patients were recruited consecutively from subjects with depression hospitalized in the Department of Psychiatry of Wroclaw Medical University. The study was based on a specially designed questionnaire. Recurrent depressive disorder was diagnosed in 45 (70.3%), a depressive episode in 9 (14.1%), and a depressive episode during the course of bipolar affective disorder in 10 (15.6%) patients. The mean duration of the current depression episode was 12.5±12.2 weeks (range 2–52 weeks). Pruritus was experienced by 11 (17.2%) patients during the depressive episode. This symptom led to scratching in all patients. Marked excoriations and erosions were found in 4 (36.4%) subjects. Five (45.4%) patients scratched their skin occasionally during the day (less that 1 h/day) and remaining 2 (18.2%) had scratching episodes lasting in total at least 3 h every day. There was no predilection site for pruritus. The severity of pruritus according to visual analogue scale (VAS) ranged between 1 and 10 points (mean 5.7±3.1 points). In all patients but one pruritus disappeared when the depressive symptoms significantly decreased. Patients with recurrent depression episodes (6 subjects) claimed that itching had occurred during every depressive episode, always in the same location, and had resolved while symptoms of depression had disappeared. Pruritus seems to be a rather common phenomenon in patients with depression and requires more attention in the future.

INDEX