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8th World Congress on Itch (WCI) 2015

September 27–29, 2015 at the Nara Kasugano International Forum IRAKA, Nara, Japan

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SUNDAY, SEPTEMBER 27TH 2015

14:00–16:30 IFSI Board meeting

17:00–17:30 Opening of the WCI
Ichiro Katayama, Japan, WCI President
Jacek C. Szepietowski, Poland, President of IFSI: The International Forum for the Study of Itch (IFSI): A successful society celebrating its 10-year anniversary

17:30–19:00 Plenary Session
Chairpersons: Yasushi Kuraishi, Japan, Ichiro Katayama, Japan
Jacek C. Szepietowski, Poland

Bernard Lecture: *Sonja Ständer, Germany:* Lessons from the Clinic: The "ice pack sign" and more (OP1)

Kuraishi Lecture: *Kenji Takamori, Japan:* Message from nerve fibers: Involvement of nerve fibers in intractable itch in atopic dermatitis (OP2)

President-invited lecture: *Ryusuke Kakigi, Japan:* Itch perception in humans (OP3)

19:00-19:20 Break

19:20–19:35 Noh Play (Japanese traditional dance)

19:45–21:30 Welcome Reception at the Venue

MONDAY, SEPTEMBER 28TH 2015

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Katsunori Yamaura, Japan: Long-term topical steroid therapy can be a probable cause for pruritus (SS1)

Plenary Session
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Masutaka Furue, Japan: New therapies for controlling atopic itch (SS6)

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17:30 Closing: Ichiro Katayama, Japan

POSTER LIST

PP1: Itch-related biting behavior and neuronal responsiveness induced by intradermal injection of pruritogens in hairless mice, *Yuhki Ueda, Kei Hashimoto, Takamichi Kitano, Kido Hiroko, Tatsumi Matsumoto, Ritsuko Ishii, Keiji Imoto, Hidemasa Furue*

PP2: **[**LEU11]-HK-1-derived peptides with D-Trp prolong antipruriceptive effects in rats, *Hideki Funahashi, Rumi Naono-Nakayama, Yu Miyahara, Yasushi Ishida, Toshikazu Nishimori*

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PP5: A neuronal brake on itch through metabotropic glutamate receptor activation, *Katarzyna Rogoz, Bejan Aresh, Fabio Batista Freitag, Hanna Pettersson, Elín Ingibjörg Magnúsdóttir, Linn Larsson Ingwall, Helena Haddadi Andersen, Chetan Nagaraja, Klas Kullander, Malin Charlotta Lagerström*

PP6: Chloroquine-induced scratching is mediated by NO/cGMP pathway in mice, *Arash Foroutan, Nazgol-Sadat Haddadi, Sattar Ostadhadi, Ahmad-Reza Dehpour*

PP7: Topical Application of DP1 Agonist Effectively Prevents Pruritus Induced by Long-term Treatment of Glucocorticoids in Allergic Contact Dermatitis Mice, *Ayaka Funakoshi, Katsunori Yamaura, Seiji Onuma, Riho Tanaka, Misako Takei, Naotomo Kambe, Hiromi Sato, Akihiro Hisaka*

PP8: Spinal PI3K-gamma activation mediates GRPR-related itching transmission in mice, *Paula Pereira, Gustavo Barroso, Giuliano Danesi, Francesca Canavese,, Vemuri Reddy, Sebastien Talbot, Maria Campos,, Ethan Lerner*

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PP20: Characterization of the Quality of Life Impact of Chronic Itch in Pediatric Patients, *Alexandra Seamens, Caitlin Greskovich, James Roberts, Suephy Chen*

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PP23: Pleiotropic action of cyclosporine on pruritus of atopic dermatitis, *Mitsutoshi Tominaga, Kyi Chan Ko, Yayoi Kamata, Yoshie Umehara, Hironori Matsuda, Nobuaki Takahashi, Katsunari Kina, Mayuko Ogawa, Hideoki Ogawa, Kenji Takamori,*

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PP35: Does uremic pruritus influence alexithymia? *Monika Heisig, Adam Reich, Jacek C. Szepietowski*

ORAL PRESENTATIONS (OP1–OP74)

BERNHARD LECTURE

OP1

LESSONS FROM THE CLINIC: THE ICE PACK SIGN AND MORE

Sonja Ständer

Center for Chronic Pruritus, Department of Dermatology, University Hospital of Münster, Germany

Chronic pruritus is a symptom of a variety of diseases and affects people of all ages. Accordingly, the patients do not present with a unique phenotype. Patients report a different severity of pruritus (including duration, intensity, quality, course and emotional burden of the symptom) and show variations in the clinical presentation of the skin. As this disparity might point to different pathomechanisms and processing of the symptom, a clinical and patient-oriented research approach offers the opportunity to gain knowledge by direct investigation of chronic pruritus patient subgroups. An interesting group is that of neuropathic pruritus, such as brachioradial pruritus (BRP). These patients report dysesthesia and itch, with a relief of the symptom by using "ice packs". Using methods originating from pain research, such as determination of intraepidermal nerve fiber density and quantitative sensory testing, we were able to identify a loss of function of cutaneous small fibers in these patients, resulting in reduced cold sensitivity. In addition, patients with qualities such as burning and stinging showed a different response than those reporting on warmth sensations alongside itching. Results from experimental cowhage and capsaicin-induced itching did not suggest that BRP patients had a peripheral sensitization of C fibers; immunohistochemical analyses excluded cutaneous inflammation. Our results suggest that peripheral nerves show secondary loss of function due to cervical compression, thus explaining the clinical phenotype of BRP.

KURAISHI LECTURE

OP2

A MESSAGE FROM NERVE FIBERS – INVOLVEMENT OF NERVE FIBERS IN INTRACTABLE ITCH IN ATOPIC DERMATITIS

Kenji Takamori[1], Mitsutoshi Tominaga[2], Atsuko Kamo[2], Yayoi Kamata[2]

[1]Institute for Environmental and Gender Specific Medicine, Juntendo University Graduate School of Medicine, [2]Department of Dermatology, Juntendo University Urayasu Hospital, Urayasu, Chiba, Japan

Itch, as well as pain, is initiated and mediated by cutaneous nerve fibers that have cell bodies in the dorsal root ganglia and trigeminal ganglia. These neurons are highly diverse in size of soma, expression of ion channels and receptors, and innervation territories. They are activated by exogenous and/or endogenous mechanical, chemical, and biological stimuli, inducing itch or pain responses. In pruritic skin diseases, including atopic dermatitis, increased nerve density in the epidermis is partly involved in itch sensitization. Nerve fibers are therefore regarded as an anti-pruritic target in dry skin-based diseases. In the Kuraishi Lecture, I deliver a message from nerve fibers gained from my basic research and translational medicine for intractable itch, especially in atopic dermatitis.

PRESIDENT-INVITED LECTURE

OP3

ITCH PERCEPTION IN HUMANS

Ryusuke Kakigi[1], Hideki Mochizuki[2]

[1]Department of Integrative Physiology, National Institute for Physiological Sciences, Okazaki, [2]The Graduate University for Advanced Studies of Life Science (SOKENDAI), Japan

We developed a new itch stimulus (i.e., electrical itch stimulus). We performed electroencephalography (EEG), magnetoencephalography (MEG) and functional magnetic resonance imaging (fMRI) recording using the electrical itch stimulus and observed itch stimulus-related brain processing. Using MEG, it was suggested that neural information related to itch was transmitted from the contralateral secondary somatosensory cortex/insula (SII/insula) to the ipsilateral SII/insula in the first stage. In addition, we also observed the activation of the precuneus. Using fMRI, we found activity in many regions such as anterior insular cortex (aIC) and motor-related regions such as supplementary motor area, basal ganglia, thalamus, cerebellum, and precuneus. Since we found the activation of the precuneus by both MEG and fMRI, we speculate that the precuneus may be important region for itch. We will also introduce our recent studies as follows: 1) The cerebral representation of scratching-induced pleasantness. We found activation in the reward system (i.e., the striatum and midbrain) and motor-related regions when pleasantness was evoked. 2) Cortico-subcortical activation patterns for itch imagery to explain 'contagious itch'. 3) A new therapy for itch using a transcranial direct current stimulation (tDCS) over the sensorimotor cortex.

NEURONAL PROCESSING OF ITCH

OP4

PHOENIXIN: A CANDIDATE PRURITOGEN IN THE MOUSE MODEL

Yi-Hung Chen[1], Alan Cowan[2], Rong-Ming Lyu[3], Siok Le Dun[2], Jaw Kang Chang[3], Nae J. Dun[2]

[1]Graduate Institute of Acupuncture Science, China Medical University, Taichung, Taiwan, [2]Department of Pharmacology and Center for Substance Abuse Research, Temple University School of Medicine, Philadelphia, [3]Phoenix Pharmaceuticals Inc., Burlingame, USA

Phoenixin (PNX) is a 14-amino acid amidated peptide (PNX-14) or an N-terminal extended 20-residue amidated peptide (PNX-20) recently identified in neural and non-neural tissues. Mass spectrometry analysis identified a major peak corresponding to PNX-14, with negligible PNX-20, in mouse spinal cord homogenate. PNX-immunoreactivity (irPNX) was detected in a population of dorsal root ganglion cells (DRGs) and in cell processes densely distributed to the superficial layers of the dorsal horn. irPNX cells and cell processes were also detected in the skin. PNX-14 (2–16 mg/kg) injected s.c.to the nape of the neck of Swiss-Webster mice provoked repetitive scratching bouts directed to the back of the neck with the hind paws. The number of scratching bouts varied from 16–95 in 30 min, commencing within 5 min post-injection and lasted about 10–15 min. Pre-treatment of mice at –20 min with nalfurafine (20 μg/kg, s.c.), the kappa opioid receptor agonist, significantly reduced the number of bouts induced by PNX-14 (4

mg/kg) compared to that of saline-pre-treated controls. Our results suggest that the peptide, PNX-14, serves as one of the endogenous signal molecules transducing itch sensation in the mouse.

OP5

RNA-SEQUENCING REVEALS A UNIQUE FINGERPRINT OF CHRONIC ITCH MEDIATORS AND RECEPTORS IN HUMANS AND PRIMATES

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The genetic profile of chronic pruritus at the peripheral level is currently under-investigated. In this study, we used RNA-seq to analyze the complete transcriptome of skin from human subjects with pruritic diseases and from a primate model of idiopathic chronic itch. Paired lesional and non-lesional skin biopsies were collected from 30 atopic dermatitis patients, 30 psoriasis patients, 40 healthy controls, and 37 Cynomolgus macaques with chronic itch. RNA-seq was performed to identify differentially expressed genes (>2.0 fold change; <0.05 FDR) in lesional versus non-lesional skin, generating an average of ~60 million paired-end 100-bp reads per sample. The RNA-seq data were correlated to patient ratings of itch intensity or to quantified primate scratching behavior. We identified over 1,000 differentially expressed genes in the lesional skin of human subjects with pruritic diseases, with ~350 genes correlating to itch severity. Similarly, over 550 genes were differentially expressed in the lesional primate skin, with ~250 genes correlating to scratching behavior. Many of these differentially expressed transcripts were associated with sensory nerve fibers, keratinocytes, mast and neutrophilic cells, and lymphocytic cells. This transcriptome has led to an increased understanding of the molecular mechanisms involved in different pruritic conditions and may provide novel targets for treatment.

OP6

NEUROPATHIC ITCH

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Nerve injuries can lead to chronic neuropathic pain or neuropathic itch. Pain and itch are generally regarded antagonistic as painful stimuli such as scratching suppresses itch and analgesic opioids generate. Based on separate specific pathways for itch and pain processing that have been identified in humans and experimental animals one would expect that neuropathic pain is based on activity in the nociceptive system whereas neuropathic itch is the result of activity in the pruriceptors according to the specificity theory for itch. However, in addition to broadly overlapping mediators of itch and pain there is also evidence for overlapping functions in primary afferents: nociceptive primary afferents can provoke itch when activated very locally in the epidermis and sensitization of both, nociceptors and pruriceptors have been found following local nerve growth factor application in volunteers. Most interestingly, expression of pruriceptive markers, such as gastrin releasing peptide, might be altered following nerve injury, such that nociceptors start to express pruriceptive mediators and could drive neuropathic itch. Thus, mechanisms underlying chronic itch and pain appear to overlap to a great extent and it will be of highest interest to compare expression patterns of primary afferents in patients suffering from neuropathic pain vs. neuropathic itch.

OP7

CYTOKINES AND ENDOTHELIN-1 CONTRIBUTE TO HISTAMIN-INDEPENDENT PRURITUS IN HUMANS

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In AD, patients suffer from increased stimulation of pruriceptors (hyperknesis) or altered stimulation by normally non-pruritic stimuli (alloknesis). We hypothesized that Interleukin-31 (IL-31) may also exert neuropoietic potential which may impact sensory nerve function in 'hypersensitive' skin of AD patients. We analyzed the IL-31-related transcriptome in sensory neurons and investigated whether IL-31 promotes sensory nerve fiber outgrowth *in vitro* and *in vivo*, in IL-31-treated and IL-31 KO mice. Transcriptional profiling of IL-31-activated DRG neurons revealed enrichment for genes promoting nervous system development, neuronal outgrowth and negatively regulating cell death. Moreover, the growth cones of primary small diameter DRG neurons showed abundant IL-31RA expression. STAT3 phosphorylation mediated IL-31-induced neuronal outgrowth and pharmacological inhibition of STAT3 completely abolished this effect. In contrast, active TRPV1 channels were dispensable for IL-31-induced neuronal sprouting. Thus, IL-31 induces a distinct transcriptional program in sensory neurons leading to nerve elongation and branching explaining for the first time the clinical observation why patients with AD experience increased sensitivity to minimal stimuli inducing sustained itch. Similarly, endothelin (ET-1) plays a significant role in histamine-independent itch. Here, we present novel data how ET-1 may contribute to peripheral itch in AD patients.

OP8

DORSAL HORN ASTROCYTES: NEW PLAYER IN CHRONIC ITCH

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Chronic itch is an intractable symptom of inflammatory skin diseases, such as atopic dermatitis. Recent studies have revealed the selective neuronal pathways for itch sensations; however, the mechanisms by which itching turns into a pathological chronic state are poorly understood. In the present study, we used mouse models of atopic dermatitis and found a long-term reactive state of astrocytes in the dorsal horn of the spinal segments that corresponds to lesioned, itchy skin. The transcription factor STAT3 was selectively activated in spinal dorsal horn (SDH) astrocytes and that conditional disruption of astrocytic STAT3 activation prevented the astrocytic activation and chronic itching, without affecting acute physiological itch. Pharmacological inhibition of STAT3 in the SDH ameliorated the fully developed chronic itch. Furthermore, atopic dermatitis mice exhibited an increase in scratching elicited by intrathecal administration of gastrin-releasing peptide, and this enhancement was normalized by suppressing STAT3-mediated reactive astrocytes. Moreover, we

identified lipocalin-2 (LCN2) as an astrocytic STAT3-dependent up-regulated factor that was crucial for chronic itch. Therefore, reactive astrocytes in the SDH with activated STAT3 play a pivotal role in chronic itch by enhancing spinal itch signaling by LCN2 and may represent a previously unrecognized target for treating chronic itch.

THE SIGs (SPECIAL INTERST GROUPS) OF IFSI

OP9

SENSITIVE SKIN: A SPECIAL INTEREST GROUP (SIG) OF THE INTERNATIONAL FORUM ON THE STUDY OF ITCH (IFSI)

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Sensitive skin can be defined as the occurrence of unpleasant sensations (stinging, burning, pain, pruritus and tingling sensations) in response to stimuli which normally not provoke such sensations. These symptoms may be accompanied by erythema or not. Sensitive skin is not only limited to the face. A new special interest group (SIG) has been initiated by the International Forum for the Study of Itch (IFSI) to answer to many questions: What is specific to itch in sensitive skin? Is sensitive skin a risk factor for developing a chronic itch? How can we assess sensitive skin and its severity? What is its epidemiology? What is its pathophysiology? How can we treat and prevent sensitive skin? Systematic reviews, consensus meetings and further new studies are scheduled.

OP10

THE SPECIAL INTEREST GROUP (SIG) OF THE INTERNATIONAL FORUM ON THE STUDY OF ITCH (IFSI) PARANEOPLASTIC ITCH

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The term "paraneoplastic itch (PI)" is used to describe itch in patients with both, hematological and solid tumor malignancies. It is considered a rare disorder but is relatively frequent in hematological malignancies. The overall prevalence and incidence is still unclear, however, chronic itch without concomitant skin changes has recently been shown to be a risk factor for having undiagnosed hematologic and bile duct malignancies. PI is frequently not recognized, either because it is disregarded, a diagnostic test does not exist or the symptoms resemble other diseases/complications. In 2012, an interdisciplinary interest group of physicians and researchers was founded. A recently published position paper reviewed the current knowledge and aimed to define what can be summarized under the term "paraneoplastic itch". The SIG concludes that PI does not receive the needed attention due to a lack of research in this field. For the future, we should try to gain more knowledge about PI in terms of pathophysiology, epidemiological data, clinical characteristics and treatment modalities. It would be interesting to know if there are any serum markers and if any malignant entities besides bile duct and hematological malignancies do show a high association as well as possible risk factors for developing PI.

OP11

QUESTIONNAIRES TO ASSESS CHRONIC ITCH: A SPECIAL INTEREST GROUP (SIG) OF THE INTERNATIONAL FORUM ON THE STUDY OF ITCH (IFSI)

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Chronic itch affecting millions of patients worldwide has a significant impact on their quality of life. The assessment of itch and its associated effects is an important component of daily clinical practice in itch management. However, it is clear that the use of a single measure does not ensure an adequate and comprehensive assessment of CI. It can become complex and burdensome to patients as the number of instruments utilized grows. Despite itch being a common complaint, there are few studies describing the use of structured questionnaires for evaluation and measurement of itch and its sensory and affective dimensions. In 2011, a Special Interest Group (SIG) was initiated by members of the International Forum for the Study of Itch (IFSI) as an interdisciplinary team to determine which of the various psychometric properties of itch questionnaires offer the greatest utility in the evaluation of chronic itch. A consensus paper addressed the expectations and unmet needs of using itch questionnaires to better assess chronic itch and guide therapy. The SIG aims to provide a template for questionnaires that could be used in different arrangements and modular configurations depending on the underlying diagnosis. Future studies should focus on disease- and population-specific questionnaire validation.

OP12

SIG UREMIC PRURITUS – WHERE ARE WE IN 2015?

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The SIG "Uremic Pruritus" (UP) was founded in 2013 when promising new therapeutic drugs were about to emerge. Unfortunately, the drugs in question were unable to meet the expectations. Nevertheless, as the initial focus of the group has always been on unmet needs of patients with UP, important questions have since been raised and new studies have been initiated. GEHIS, the first representative cross-sectional study in UP has been launched by German scientists and has generated quite a number of interesting

new data on UP. These findings prompted the scientific community to cast a fresh look on UP as a disease entity. A position paper on this topic is being prepared. At present, a couple of further studies are under way. Besides the question on the prevalence of UP in patients with chronic renal insufficiency before dialysis is started and in patients after kidney transplantation, new studies deal with the mechanisms by which itch is induced in renal insufficiency. The role of calcium-binding proteins, skin-salt accumulation and the status of oral health in UP are also currently under investigation.

INFLAMMATION

OP13

DISTINCT ROLES OF NEUROPEPTIDES IN PRURICEPTIVE PROCESSING IN THE SPINAL CORD

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Neuropeptides are key messages for relaying pruriceptive information from the periphery to the spinal cord. Unlike classical neurotransmitters (e.g. glutamate), neuropeptides have been considered as modulators rather than mediators. Recent studies have implicated neuromedin B (NMB) and gastrin-releasing peptide (GRP) in primary afferents in mediating histamine and chloroquine (CQ) itch, respectively, via NMBR and GRPR in the spinal cord. Pain behavioral analysis of NMB/GRP or GRPR/NMBR double-knockouts indicates that neither NMB-NMBR nor GRP-GRPR signaling is required for nociceptive processing. Moreover, we found that B-type natrineurietc peptide (BNP), which activates NPRA receptor encoded by Npr1 gene, modulates histamine and CQ itch by potentiating NMB-NMBR and GRP-GRPR signaling. In contrast, neither NMB nor GRP can facilitate histamine or CQ itch. These data strongly suggest that NMB and GRP are itch-specific mediators and reveal important functional differences between modulators and mediators in pruriceptive processing. Identification of itch-specific neuropeptide provides us a unique opportunity to unravel how pruriceptive information is received, differentiated, processed and encoded in the spinal cord.

OP14

THE PHYSIOLOGIC ROLE OF IgE AND SCRATCHING IN NEGATIVELY REGULATING INNATE IMMUNE RESPONSES

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Scratching and IgE are considered to be deleterious for the host. Here we propose the alternative view that IgE and scratching may be a strategy evolutionally selected as a negative feedback mechanism to counter-regulate the detrimental consequences induced by excessive activation of innate immune responses. Immediate-type hypersensitivity (ITH) reactions are elicited by application of hapten to the ear, which is subject to hindlimb scratching, indicating a need for a careful dissection of the effects of hapten exposure and scratching. We show that initial hapten exposure to the site free from scratching results in Toll-like receptor (TLR) 2-dependent rapid swelling showing a time course similar to that of IgE-mediated ITH, and mast-cell degranulation. This hapten-induced, TLR2-dependent ITH-like response can be inhibited by hapten-specific IgE, while such IgE is essential for eliciting hapten-specific ITH in the ear subject to hind limb scratching. This inhibitory role of hapten-specific IgE on TLR2-dependnet mast cell activation is confirmed in mast cell knock-in mice reconstituted with cultured bone marrow-derived mast cells. IgE may have originally evolved to deal with innate immune responses and scratching would permit otherwise homeostatic signals that can inhibit TLR2-dependnetn mast-cell activation, to initiate harmful IgE-dependent activation cascades.

OP15

MUTUAL UP-REGULATION OF ENDOTHELIN-1 AND IL-25 IN ATOPIC DERMATITIS

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Endothelin 1 (ET-1) has been reported to evoke histamine-independent pruritus in mammals. However, its association with pruritus or inflammation of atopic dermatitis (AD) has not been clarified. We sought to investigate the role of ET-1 in the skin inflammation of AD. To examine the role of ET-1 in AD, we investigated the expression of ET-1 and IL-25 in the skin of an AD mouse model and AD patients, and examined the mutual regulatory relationship between ET-1 and IL-25, one of the important cytokines in AD, using the human HaCaT keratinocyte cell line. We immunohistochemically confirmed the up-regulation of ET-1 and IL-25 expression in the epidermis of both the AD mouse model and AD patients. In vitro, IL-25 up-regulated ET-1 mRNA and protein expression in a concentration- and time-dependent fashion in HaCaT cells. This IL-25-induced ET-1 expression was inhibited by ERK1/2 or JNK inhibitor. In a reciprocal manner, ET-1 also induced IL-25 up-regulation. The enhancing effect of ET-1 on IL-25 was inhibited by an endothelin A receptor antagonist, ERK1/2 inhibitor or p38 inhibitor. These findings suggest that mutual up-regulation of ET-1 and IL-25 takes place in the epidermis in AD, which may be a future target for anti-pruritic agents.

OP16

α-MELANOCYTE-STIMULATING HORMONE INDUCES ITCHING IN MICE: INVOLVEMENT OF THE HISTAMINE RELEASED FROM EPIDERMAL KERATINOCYTES

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Itching is usually accompanied by pigmentation in the lesional skin of sunburn, wound repair and chronic renal failure with hemodialysis. A number of studies have shown that the α-melanocyte-stimulating hormone (α-MSH) produced by external stimuli, such as ultraviolet irradiation induces cutaneous pigmentation. However, it is unclear whether α-MSH is also involved in the itching. In this study, we found that an intradermal injection of α-MSH

induced scratching in mice. The α-MSH-induced scratching was inhibited by the μ-opioid receptor antagonist naltrexone hydrocholoride and the H1 histamine receptor antagonist terfenadine. In mast cell-deficient mice, α-MSH also elicited scratching, which was inhibited by terfenadine. The immunoreactivity for L-histidine decarboxylase (HDC), a key enzyme required for the production of histamine, histamine and the melanocortin 1 and 5 receptors (MC1R and MC5R) were shown in not only mast cells, but also keratinocytes in murine skin. In addition, the mouse keratinocyte cell (Pam212) also showed the immunoractivity for HDC, histamine, MC1R and MC5R. The application of α-MSH induced the release of histamine from Pam212. These findings indicate that α-MSH may play an important role in the itching associated with pigmented cutaneous lesions, and that the histamine released from keratinocytes is involved in this α-MSH-induced itching.

OP17

INVOLVEMENT OF BASOPHILS IN SPONTANEOUS ITCH-RELATED RESPONSES IN MICE WITH ATOPY-LIKE DERMATITIS

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Atopic dermatitis is a chronic inflammatory skin disease characterized by severe itch. However, detail understanding of the mechanisms of the itch is limited. Basophils are well-known as multifunctional immune cells. Recent studies have demonstrated that basophiles play an important role in chronic allergy. Therefore, we examined whether basophils were involved in spontaneous itch-related responses in mice with atopy-like dermatitis. In this study, we used male NC/jic mice with severe dermatitis bred under conventional condition. In a part of experiments, healthy NC/jic mice bred under specific pathogen free condition were used. The number of basophils was increased significantly in the skin of mice with dermatitis, compared with that in healthy mice. The treatment with basophil-depleting antibody (Ba103) inhibited spontaneous scratching in mice with dermatitis. Our previous reports have shown that serine protease and proteinase-activated receptor 2 (PAR2) are involved in spontaneous scratching in mice with dermatitis. Basophils release serine protease mMCP-11. An intradermal injection of mMCP-11 elicited scratching, which was inhibited by the PAR2 neutralizing antibodies, in healthy mice. Taken together, it is suggested that basophils is involved in the spontaneous scratching in mice with dermatitis. mMCP-11 may be one of the itch mediators released from basophils.

OP18

A VISCERAL REPRESENTATION OF ITCH: IDENTIFICATION OF 'ITCH-SPECIFIC' PRURITOGENIC MECHANISMS WITHIN COLONIC SENSORY PATHWAYS

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Itch, like pain, is a major protective mechanism. Pain arises from both skin and viscera; we investigated whether 'itch-specific' mechanisms have functions within visceral pathways. We assessed healthy mice and those with chronic visceral hypersensitivity (CVH), and in mice over-expressing bile acid receptor TGR5 (tgr5-tg) or lacking either TGR5 (tgr5-/-) or TRPA1 (trpa1-/-). In single colonic DRG RT-PCR, mRNA for TGR5 (15%), MrgprA3 (33%), MrpgrC11 (33%), GRP (20%), NPPB (20%), TRPA1 (43%) and TRPV1 (64%) was detected. We detected protein expression of TGR5, MrgprA3, and MrgprC11 in colonic mucosal epithelium. These receptors were co-localized with TRPA1, TRPV1, gastrin-releasing peptide, and natriuretic poly-peptide B. In *ex vivo* and *in vivo* functional studies, TGR5 agonists excite colonic afferents and amplify responses to mechanical stimuli, consistent with neuronal sensitization. Effects were greater in tgr5-tg mice, and lost in tgr5-/- and trpa1-/- mice. Chloroquine and BAM8-22 excited colonic afferents and caused activation of dorsal horn neurons. In summary, CHV mice showed sustained amplification of irritants to activate and sensitize colonic sensory neurons, suggesting functional up-regulation of this signaling pathway which increased responsiveness to known pruritogens. We propose colonic irritant sensing system is a visceral representation of somatic itch pathway, and contributes to sensory disturbances that accompany intestinal disorders.

NEW ANTIPRURITIC THERAPY

OP19

ANTIHISTAMINES IN THE TREATMENT OF PSORIATIC PRURITUS? DOUBLE-BLIND, PLACEBO-CONTROLLED PILOT STUDY

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Pruritus, often described as the most burdensome symptom, affects 70–90% of psoriasis patients. We performed a study to evaluate the efficacy of antihistamines in reducing itch in psoriasis. Sixty one patients were randomized into group 1 (n=20) – clemastine 2×1 mg/day for 6 days, group 2 (n=21) – levocetirizine 1×5 mg in the evening and 1× placebo in the morning for 6 days, group 3 (n=20) – placebo twice daily one tablet for 6 days. All patients received the same routine treatment of psoriatic skin lesions. Patient evaluated itch intensity according to VAS and the Itch Questionnaire. An accelerometer was worn for 6 consecutive nights to measure the hand movements during sleeping. There was statistically significant decrease of mean VAS scoring in clemastine and levocetirizine group (p<0.001) but not in placebo group. Questionnaire scoring decreased significantly during the study in all groups. The greatest decrease was seen in clemastine group with 4.5±3.3 points (p<0.0001). The number of wrist movements during sleep did not differ significantly between groups. Antihistamines of both first and second generations seem to be effective in reducing itch in patients with plaque type psoriasis. These observations need to be confirmed on the larger group of patients.

OP20

TO REPORT EFFICACY RESULTS FROM AN 8-WEEK PHASE 2 STUDY TREATING ADOLESCENTS AND ADULTS WITH MILD TO MODERATE ATOPIC DERMATITIS TREATED WITH 0.3% AND 1% OPA-15406 OINTMENT

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OPA-15406 is a selective type-4 phosphodiesterase (PDE4) inhibitor developed for treatment atopic dermatitis (AD). *Objectives:* To evaluate efficacy of 0.3% and 1% OPA-15406 compared with vehicle when administered topically BID over 8 weeks. *Methods:* This Ph2, randomized, double-blind, vehicle-controlled, dose-ranging, study enrolled 121 subjects 10–70 years with AD. Baseline disease severity was defined by Investigator Global Assessment (IGA) score of 2 (mild) or 3(moderate). Efficacy was evaluated by IGA with 2-grade change from baseline at W4 and W8, Eczema Area Severity Index (EASI) change and pruritus assessed with Visual Analog Scale (VAS). *Results:* IGA success rate with a 2-grade reduction was 15% for 0.3% (12.3% difference to vehicle [p=0.0617]) and 20.9% for 1% (18.2% difference [p=0.0165]). The change from baseline EASI in 1% was significant over vehicle as early as W1 (–1.78; p=0.0098) and sustained significance at W4 (–2.56; p=0.0176) and W8 (–2.36; p=0.047). Additional analysis of individual EASI components for 1% demonstrated improvement in excoriation. Change from baseline VAS score in 1% OPA-15406 was significant over vehicle at W1 (–17.25; p=0.0004) and sustained significance at W4 (–11.54; p=0.0452) and W8(–13.05; p=0.0432). *Conclusions:* 1% OPA-15406 demonstrated rapid pruritus relief and significant improvements in disease severity over vehicle at W4 which sustained up to W8.

OP21

DEVELOPMENT OF ASIMADOLINE, A SELECTIVE KAPPA OPIOID RECEPTOR AGONIST, FOR THE TREATMENT OF PRURITUS

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Available mechanistic, preclinical, and clinical data indicate that kappa opioid receptor agonists may be broadly effective for the treatment of chronic itch. Asimadoline is an orally active, highly selective kappa-opioid receptor agonist with approximately 500-fold greater affinity for human kappa-, as compared with either delta- or mu-opioid receptors. Asimadoline has been tested in >1,900 human subjects for indications other than pruritus and demonstrates an acceptable safety profile. Asimadoline has also been tested in several preclinical animal models of pruritus. Results from a series of preclinical studies indicate that asimadoline, given prior to dosing with the inflammatory pruritogen Substance P or with histamine, results in inhibition of scratching behavior and that these effects are dose-related. Asimadoline is currently being tested in a double-blind, placebo-controlled Phase 2 Proof-of-Concept clinical study designed to evaluate the safety, tolerability, and clinical efficacy in patients with pruritus associated with atopic dermatitis. Approximately 200 patients will be treated in a 1:1 ratio with asimadoline or placebo for 4 weeks, followed by an open-label extension phase for 4 weeks, and will be evaluated for safety and tolerability, plasma pharmacokinetics, and pruritus and atopic dermatitis efficacy measures.

OP22

AN INVESTIGATIONAL STUDY OF TRADIPITANT FOR THE TREATMENT OF CHRONIC PRURITUS IN PATIENTS WITH ATOPIC DERMATITIS

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Pruritus represents one of the most burdensome symptoms of atopic dermatitis (AD) impacting quality of life. Substance P is believed to mediate chronic pruritus (CP). Tradipitant is a potent inhibitor of human cell membrane NK-1 receptor binding *in vitro* and shows promise as a potential treatment for CP in AD. Sixty-nine AD patients with CP were randomized in VP-VLY-686-2101 to double-blind tradipitant or placebo nightly for 4 weeks. Both arms demonstrated significant improvement from baseline itch measured on a 100 mm VAS. In skin biopsies, NK1 receptor expression and epidermal nerves did not significantly differ between treatment groups. Despite the lack of a statistical difference between arms, a significant correlation was seen between increasing blood levels of tradipitant and increasing VAS improvement in tradipitant-treated patients. A separate post-hoc analysis of time of assessment allowed stratification into two distinct groups – subjects with pruritus assessments in the morning (AM; higher levels of tradipitant) and in the afternoon (PM; lower levels of tradipitant). In the AM group, treatment with tradipitant (n=18) had significant and clinically meaningful effects as compared to placebo (n=17) on multiple efficacy outcomes (p<0.01 to p<0.05). Identical analysis in the PM group showed no significant difference between treatment arms.

OP23

5-HT7 RECEPTORS: A NOVEL THERAPEUTIC TARGET FOR THE TREATMENT OF PRURITUS

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Serotonin (5-HT), modulate pruritic process via interaction with their receptors, which exist not only in the skin but also in the central nervous system. While the previous studies provide evidence that 5-HT1, 5-HT2 and 5-HT3 receptors have been participate in the processing of pruritus, there is no study evaluating the role of 5-HT7 receptors in pruritus. In this study, we explored the contribution of 5-HT7 receptor system in the peripheral sites and spinal level in the itch modulation using male Balb-C mice. Intradermal injection of selective 5-HT7 receptor agonist LP 44, LP 211 and AS 19 (5, 25, 50, 100 μg in a volume of 50 μl) into the rostral part of skin on the back induce dose dependent scratching behaviour which were totally reversed by either systemic (10 mg/kg, i.p.) or intrathecal (10 μg) injection of SB 269970, a selective 5-HT7 receptor antagonist. Systemic (10 mg/kg) and intrathecal (10 μg) administration of SB 269970 also blocked intradermal 5-HT (25 μg), compound 48/80 (100 μg) and histamine (200 μg) induced scratches. Our data suggests that 5-HT7 receptors play a crucial role in the pruritus at peripheral and spinal level and 5-HT7 receptor antagonists look promising novel antipruritic agents.

OP24

USE OF PLACEBO EFFECTS FOR INNOVATIVE TREATMENT STRATEGIES IN ITCH

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Physical complaints, such as itch or pain, can be effectively altered by placebo effects, due to induction of expectations of a possible beneficial treatment outcome ("Pain already reduces when seeing the painkiller"). The same is true for nocebo effects which are induced by expectations of a possible unfavorable treatment outcome or side effects. The major clinical challenge remains whether experimentally laboratory findings of induced placebo and nocebo effects can be used as therapeutic strategies to improve treatment outcomes. In the presentations, recent results will be presented to demonstrate a) the evidence for placebo and nocebo effects in itch, b) what are the most effective methods to induce placebo and nocebo effects in itch as well as c) whether nocebo effects – once induced–can be changed. Results have several implications for the treatment of patients with itch problems in clinical practice. Treatment outcomes might be maximized by making optimally use of placebo effects in clinical practice, by using both conscious and automatic strategies of optimizing expectancy effects, for example, by applying conditioning principles for therapy adherence, adjusting environmental cues to the preferred outcome strategies or replacing regular pharmacological treatments partly by expectancy interventions.

METHODOLOGY FOR ITCH RESEARCH

OP25

PSYCHOPHYSIOLOGICAL PROCESSING OF ITCH IN PATIENTS WITH PERSISTENT POST-BURN ITCH

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Almost all burn-injured patients experience itch, of whom a substantial proportion develops persistent itch, which can severely affect quality of life. In line with research in chronic pain, different psychophysiological processes, of which central sensitization, conditioned modulation, and attentional processes have been studied most frequently, are assumed to play a role in chronic itch. However, these processes have barely been investigated with regard to persistent post-burn itch. In this study, 15 patients with persistent post-burn itch and 15 matched healthy controls were included. Quantitative sensory testing stimuli were applied to investigate sensitivity to itch and conditioned itch modulation. Attentional processing of itch was investigated with a frequently used attention task. Additionally, electroencephalography (EEG) measurements were carried out. The patients displayed a marginally significantly higher sensitivity towards mechanical and histamine stimuli than control subjects. There were no indications that conditioned itch modulation or attentional processing of itch were altered in the patients compared to the controls. EEG data have not been analyzed yet. Psychophysiological processes shown to contribute to chronic itch and pain seem to be only partially involved in persistent post-burn itch. Clarifying the processes underlying persistent post-burn itch contributes to early identification and treatment of patients developing persistent itch.

OP26

COMPARISON OF THREE ITCH-INDUCING METHODS: DIFFERENCES IN INTENSITY, EMOTIONAL APPRAISAL, LOCALIZATION AND QUALITY OF EVOKED ITCH

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Background: Different stimuli are used to induce itch (cowhage, histamine, audio-visual itch stimuli). This study compared the intensity, emotional appraisal, localization and quality of itch evoked by cowhage, histamine and audio-visual stimuli. *Methods:* Itch was induced in 200 healthy subjects by different methods. Cowhage + non-itch-inducing skin video (NISV; G1: n=20); histamine + NISV (G2: n = 40), placebo + itch-inducing video (IIV; G3: n=60); sensitizing skin-video + histamine + NISV (G4: n=40); sensitizing skin-video + placebo + IIV (G5: n=40). Itch intensity was measured by VAS (0–10). Localization, quality and emotional appraisal were measured by questionnaires. *Results:* The absolute itch intensities in descending order were: G1 (6.2±3.6), G4 (5.2±3.0), G2 (4.9±3.1), G5 (4.0±3.0), G3 (2.8±2.6). The itch increase in descending order was G1 (5.5±3.8), G2 (4.5±3.2), G4 (3.1±3.0), G5 (3.0±2.8), G3 (1.7±2.6). Non-inferiority tests showed that after sensitization, itch intensity evoked by histamine and audio-visual stimuli are equal, but there were differences regarding the quality, localization and emotional appraisal of induced itch. *Conclusion:* After sensitization, audio-visual stimuli and histamine are equally effective to induce itch, but audio-visual itch stimuli lead to a different localization, quality and emotional appraisal of itch.

OP27

MEASURING PEDIATRIC PRURITUS: CAN PROVIDERS OR PARENTS BE PROXIES?

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Introduction: A lack of validated pediatric itch scales often leaves parents and providers to approximate a child's itch severity. In response, we have developed the ItchyQuant, a cartoon version of a traditional numeric rating scale for pruritus severity. *Methods:* Twelve children between 4–17 years old with chronic pruritus were recruited from Emory Clinic. The child, parent, and provider were asked to rate the child's itch on the ItchyQuant. A Friedman test with *post hoc* Bonferroni corrected Wilcoxon sign-rank tests were performed to determine if differences existed between each

individual's itch rating. *Results:* There was a statistically significant difference between groups as determined by the Friedman test, p=0.01. *Post hoc* comparisons indicated that the difference between provider (mean 2.54, SD 2.47) and child (mean 5.46, SD 2.69) itch rating was significant, p=0.004. The difference between provider and parent (mean 5.96, SD 2.77) was also significant, p=0.006. There was no significant difference between parent and child. *Conclusion:* Providers rate itch as significantly less severe than both pediatric patients and their parents. A larger study population and further investigation is needed to better understand this difference. However, our pilot data suggests that providers should be aware of this underrating phenomenon when treating itchy pediatric patients.

OP28

PATIENT BENEFIT INDEX: PRURITUS (PBI-P) IS A HIGHLY VALUABLE TOOL FOR THE ASSESSMENT OF ANTIPRURITIC TREATMENT EFFICACY

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Analysis of treatment benefits achieved by patients is of great importance for health-care providers and insurance companies. We aimed to evaluate the Patient Benefit Index – Pruritus (PBI-P) as a novel tool assessing the antipruritic treatment efficacy from the patients' perspective. A total of 75 patients (29 women and 46 men) suffering from chronic dermatological pruritus were included. All patients assessed their pruritus severity using VAS, NRS, VRS, and Itch Severity Questionnaire and completed the HADS, DLQI and Patient Needs Questionnaire (PNQ) – the latter the first part of PBI-P. All assessments were repeated after antipruritic treatment completion, but the Patient Benefit Questionnaire (PBQ) was completed instead of the PNQ this time. Based on PNQ and PBQ values a weighted PBI-P benefit score was calculated for each patient. Mean PBI-P was 2.1±0.9 points (range: 0.02–4.0 points). The value of PBI-P significantly correlated with pruritus improvement (ρ=0.22 to 0.26, p<0.01), quality of life improvement (ρ=0.24, p<0.01), post-treatment pruritus intensity (ρ=–0.31 to –0.28, p<0.01), as well as level of depressive symptoms (ρ=–0.24, p<0.01) and quality of life at the end of treatment period (ρ=–0.24, p<0.01). Based on our results we can conclude that PBI-P permits valid evaluation of patient-relevant benefits during antipruritic treatment.

OP29

EXPRESSION OF INTERLEUKIN 31 IN LESIONAL SKIN OF LICHEN PLANUS HAS NO INFLUENCE ON PRURITUS

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Background: Pruritus is one of the major features of lichen planus (LP), however, its pathogenesis remains largely unknown. Objective: The aim of our study was to analyze the role of IL-31 in the pathogenesis of pruritus in LP. *Materials and Methods:* The study group included 22 patients with LP. Control group consisted of 14 healthy volunteers. All subjects underwent thorough examination. Pruritus severity was evaluated with the visual analogue scale (VAS) and the 12-item Itch Questionnaire. IL-31 expression in the skin was assessed using semiquantitive immunofluorescence analysis. *Results:* Pruritus maximal intensity according to VAS was 6.5±2.7 points and according to the 12-item Itch Questionnaire 6.9±2.8 points. Lesional LP skin showed significantly higher IL-31 expression compared to healthy skin (p<0.001). The most abundant immunofluorescence was observed within granular layer. However, there was no correlation between expression of IL-31 and pruritus intensity assessed according to VAS (VASmax: ρ=–0.08, p=0.73), as well as 12-item Itch Questionnaire: ρ=–0.11, p=0.65). *Conclusions:* Pruritus is a very common symptom of LP. For the first time we have demonstrated that IL-31 is overexpressed in the lesional skin of LP but its expression does not correlate with intensity of pruritus.

ANIMAL MODELS OF ITCH

OP30

A NEW MOUSE MODEL OF ATOPIC DERMATITIS CHARACTERIZED BY SEVERE AND CHRONIC ITCH

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Atopic dermatitis (AD) is a common skin disease associated with skin barrier defects and abnormal immune responses. Chronic itch is a hallmark of AD, but its etiologic mechanisms are not fully understood. The aim of this study was to establish an itch model reflecting AD pathology. To induce barrier-defective dry skin in mice, hairless mice were provided with a special diet deficient in polyunsaturated fatty acids and starch. Furthermore, after development of the dry skin symptoms, ointment containing mite extract was repeatedly applied to the back and facial skin of mice. Compared with normal mice, dry skin mice exhibited scratching behavior and skin inflammatory changes including epidermal thickening and mast cell hyperplasia. When the barrier-defective dry skin was repeatedly exposed to mite antigens, the barrier function was further exacerbated; marked scratching behavior and excoriations were observed; the number of dermal eosinophils was significantly increased; Th2-related cytokines, such as thymic stromal lymphopoietin, interleukin (IL)-4, and IL-13, were detected in the lesional skin. On the other hand, the mite exposure in normal mice caused no apparent symptoms. In conclusion, this model could be useful for studying the mechanism of severe and chronic itch accompanied by AD.

OP31

INTRATHECAL MINOCYCLINE ATTENUATES ITCH IN ATOPIC DERMATATIS MOUSE MODEL

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Itch is transmitted from the primary afferents to dorsal horn of spinal cord, and then brain recognizes itching. In this process,

intractable chronic itch may be occurred by abnormal neuronal firing in both the periphery and central nervous system. Recently, it has been demonstrated that spinal glial cells such as microglia and astrocytes are involved in modulation of neuropathic pain. However, roles of spinal glial cells in intractable itch such as atopic dermatitis (AD) are currently unknown. This study was conducted to examine antipruritic effect of lumber intrathecal administration of minocycline, an inhibitor of microglial activation, in an AD model NC/Nga mouse. Dermatitis of mice was induced by application of Dermatophagoides farinae body (Dfb) twice a week for 3 weeks, and AD model mice showed significant loss of transepidermal water and more scratching bouts. We next intrathecally administrated minocycline (5 or 50 μg/5 μl) three times a week for 2 weeks, and continued applying Dfb twice a week for maintenance of the AD-like condition. Intrathecal administration of minocycline dose-dependently suppressed scratching bouts in AD model mice, and also improved the dermatitis in the minocycline-treated group. These findings suggest that spinal microglia may be a therapeutic target for intractable itch of AD.

OP32

MOUSE MODEL OF PSORIATIC ITCH

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Itch is the major symptom of psoriasis, but the underlying mechanisms behind this symptom are largely unknown. To investigate the neuronal mechanisms of psoriatic itch, we have developed an animal model. To assess spontaneous scratching, mice were videotaped, and the number of spontaneous scratch bouts was counted. To test for alloknesis (touch-evoked itch), a weak von Frey filament (VF; 0.7 mN) was repeatedly applied to psoriatic skin, and the presence or absence of an evoked hind limb scratch bout was noted. VF stimulation does not elicit any response in naïve C57BL/6 mice. The psoriasis model exhibited scaly skin lesions as well as thickened epidermis and epidermal nerve elongation. The mRNA levels of psoriasis-associated cytokines, such as IL-17A, IL-17F, IL-22, and IL-23, were significantly increased. Our model of psoriatic itch displayed a time-dependent increase in both spontaneous and VF-evoked scratching. This new animal model appears to be useful for investigations of itch and possible underlying mechanisms involving sensitization of itch-signaling pathways in psoriasis.

OP33

HEAT-PROVOKED ITCH IN ATOPIC DERMATITIS: THE POSSIBLE ROLE OF ARTEMIN IN CENTRAL NERVOUS SENSITIZATION TO WARMTH

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Patients with atopic dermatitis frequently complain that warm environment frequently exacerbate their pruritus. However, its molecular mechanisms remain obscure. Previously, we reported the peculiar function of artemin, which is expressed in substance P-treated dermal fibroblast, and accumulated in upper dermis of lesional skin of atopic dermatitis. Artemin increased thermal susceptibility of skin. Moreover, mice received subcutaneous injection of artemin exhibited abnormal behavior such as wiping of their whole body at an environmental temperature of 38 degree. These results indicated that topically accumulated artemin in skin might induce the systemic thermal hypersensitivity of skin. We speculated that artemin accumulated in lesional skin might sensitize the central nervous system sensitization against heat stimulus. To investigate the cerebral excitation of artemin-injected mice, we employed the manganese-enhanced magnetic resonance imaging (MEMRI) strategy. MEMRI found the synergistic cerebral excitation in artemin-injected mice by the heat stimulus. Furthermore, administration of artemin-neutralization antibody suppressed this excess cerebral excitation. Artemin was thought to be a novel therapeutic target for heat-provoked itch in atopic dermatitis.

SIG (SCORING ITCH IN CLINICAL TRIALS)

OP34

CUT-OFF VALUES OF THE VISUAL ANALOGUE SCALE (VAS) AND NUMERIC RATING SCALE (NRS) IN PRURITUS ASSESSMENT

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The visual analogue scale (VAS) and numeric rating scale (NRS) have been used for a long time for assessment of pruritus intensity. Some years ago we have proposed a set of cut-off values of VAS to distinguish between mild, moderate, severe, and very severe pruritus on the basis of a small collective analysis. Now, we performed an in depth analysis of data of 5610 patients with chronic pruritus including VAS and NRS assessment of their first visit in our center. We found that the cut offs for 3-7-9 provided both high Cohen's kappa coefficient (VAS: 0.692 (0.678–0.706) K (95% CI), r=0.803; NRS: 0.649 (0.634–0.664 K (95% CI), r=0.794) and reliable mean values (mild pruritus, average VAS/NRS: 1.4±0.7/1.6±0.5; moderate pruritus: 4.7±1.1/4.3±1.1; severe pruritus: 7.8±0.6/7.5±0.5; very severe pruritus: 9.6±0.4/9.5±0.5) in the investigated collective. Accordingly, taking into account our own results and available literature data it seems that the most appropriate set of cut-off values for both VAS and NRS is 3-7-9, which means that values >0 but <3 points represent mild pruritus, values of ≥3 but <7 points – moderate pruritus, ≥7 but <9 points – severe pruritus, and ≥ 9 points – very severe pruritus.

OP35

VALIDATING THE ITCHYQUANT: A SELF-REPORT ITCH SEVERITY SCALE

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Introduction: The ItchyQuant is a self-reported numeric rating scale for itch severity that incorporates cartoons depicting various severities of itch. We evaluate the concurrent validity of

this scale in adults with pruritus. *Methods:* A total of 74 subjects were recruited from four clinical sites (Emory, Oregon Health and Science University, Temple, Rush). Patients were asked to rate their itch on a traditional 11-point numeric rating scale (NRS) and the ItchyQuant. Survey administration order was randomized. Spearman's correlation coefficients were determined to assess concurrent validity between the NRS and ItchyQuant. Patients were also asked which scale they preferred and/or found easier; a Wilcoxon signed rank test was used to determine statistical differences. *Results:* The ItchyQuant scale showed a high correlation with the NRS (r=0.91, $p<0.0001$). 49% of patients preferred the ItchyQuant, while only 24% preferred the NRS and 27% had no preference ($p=0.02$). 47% of patients reported the ItchyQuant was easier to use, while only 21% reported the NRS was easier to use and 31% had no preference ($p=0.01$). *Conclusions:* The ItchyQuant is a reasonable scale to use for self-reported pruritus severity given the preference and ease of use reported by our sample and high correlation to the NRS.

OP36

THE ePRO APPLICATION ITCHAPP© PROVIDES RELIABLE DOCUMENTATION OF ITCH IN CLINICAL TRIALS

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To solve the problem of patients non-compliance with paper based diaries on the one and the subjectivity of itch on the other hand, the ItchApp©, an enhanced E-Diary designed for Android smartphones, was developed. Pruritus can be obtained every day via numeric rating scale, verbal rating scale and additional questions related to the dynamic of the symptom. ItchApp© is currently used in various clinical trials including a completed validation study. Data from 55 patients who participated in a randomized, placebo-controlled clinical trial using the ItchApp© and completes questionnaires regarding the validity and feasibility of this application were analyzed. None of the patients had issues in the use of the application, only two of them proposed to enlarge the font size of the smartphone. 98.1% think that the questions were easy to understand. Besides this a high compliance was found: 87% of the patients used ItchApp© regularly on a daily basis and none of the patients had skipped any questions, regardless of gender and age. In summary, the ItchApp© is a reliable application to record the course of itch in clinical trials.

OP37

EUROPEAN EADV NETWORK ON ASSESSMENT OF SEVERITY AND BURDEN OF PRURITUS (PRUNET)

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Various methods are employed in the daily clinical practice of different countries in order to assess pruritus in dermatoses, often resulting in difficulties comparing collected data. With the support of the EADV, we founded a European Network on Assessment of Severity and Burden of Pruritus (PruNet). Our 28 PruNet experts from 15 EU countries, consisting of 21 dermatologists, 5 medical informaticists and 2 psychologists, all share the common goal of unifying and standardizing itch assessment in routine dermatological care. During the first consensus conference, it was agreed that tools for measuring itch intensity (ex. The visual analog scale) and quality of life (ex. ItchyQol) are of primary importance and should urgently be foremost validated.

OP38

VALIDATION OF THE JAPANESE VERSION OF THE 5D-ITCH SCALE IN ADULT PATIENTS WITH ATOPIC DERMATITIS

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The 5-D itch scale (5D) was developed as a self-administered questionnaire consisting of 5 domains of itch such as duration, degree, direction, disability and distribution. We here report the validation of the Japanese version of 5D (5D-J). The 5D-J was created following the standard protocols of forward/backward translation with pretest. A total of 169 adult patients with atopic dermatitis (AD) participated in the study to test the reliability, validity and responsiveness of the 5D-J. The 5D-J score correlated significantly with visual analogue scale (VAS) score of itch intensity (r=0.666, $p<0.0001$), with severity scoring of atopic dermatitis (SCORAD) of the skin lesion (r=0.385, $p<0.0001$), and with dermatology life quality index (DLQI) (r=0.671, $p<0.0001$). Internal consistency and test-retest reliability were satisfactory. Changes in 5D-J score over the course of 4 to 12 weeks correlated well with those of VAS suggesting a good responsiveness. Patients' evaluation revealed that it took 3.5 ± 2.1 minutes to complete 5D-J and they found it easier to express the extent of itch compared to VAS. We conclude that the 5D-J seems to be a reliable tool to measure itch in adult patients with AD.

ITCH CLINIC

OP39

AN EVIDENCE-BASED REVIEW OF SYSTEMIC TREATMENTS FOR ITCH.

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Background and objective: Many treatment modalities are used for itch treatment without adequate evidence of their efficacy. *Databases and data treatment:* We performed a systematic review and, when appropriate, meta-analysis from available placebo-controlled randomized controlled trails (RCTs). A systematic search of the literature was performed. The primary outcome was the change in the itch score comparing the intervention group and placebo group. *Results:* Twenty-six eligible RCTs were included. We found evidence for the effectiveness of: naltrexone (in cholestatic itch and atopic eczema), nalfurafine (in uremic itch), gabapentin (in uremic itch), and ursodeoxycholic acid (in intrahepatic cholestasis of pregnancy). The results of 2 RCTs with naltrexone in itch are conflicting. On the other hand, we did not find any benefit from ondansetron (in cholestatic and uremic itch), ergocalciferol (in uremic itch), colesevelam (in cholestatic itch), or gabapentin (in cholestatic itch). The possible effectiveness of sertraline,

paroxetine, cromolyn sodium, zinc sulfate, omega-3 fatty acid, montelukast, doxepin, and rifampin need to be confirmed from future large studies. *Conclusions:* The findings from this study suggest that there are select agents that may help itching. The major limitations are that there are small numbers of available RCTs and methodological differences across studies.

OP40

ITCH AS AN IMPORTANT CLINICAL SYMPTOM OF PSORIASIS

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Psoriasis is one of the most common chronic inflammatory skin diseases, found in about 1% to 3% of general population. For a long time psoriasis was considered as a non-pruritic dermatosis. However, a number of studies, mostly performed within the last 20 years, clearly documented that pruritus is a very prevalent symptom of psoriasis affecting 70–90% of patients suffering from this disease. Pruritus can be limited to psoriatic plaques, but in many subjects may also affect uninvolved skin. The mean severity of pruritus assessed according to visual analog scale (VAS) ranged from 4.2 to 6.4 points, indicating that most patients suffer from pruritus of moderate severity. The patients consider pruritus as the most bothersome symptom of the disease and as the most important factor contributing to psoriasis severity. Pruritic psoriatic individuals present lower quality of life, higher level of stigmatization and are more depressed. The pathogenesis of pruritus in psoriasis is still not completely clear, but the neurogenic inflammation probably plays a crucial role. Increased innervation density and abnormal neuropeptides homeostasis is taken into consideration. It is also suggested that pruritus in psoriasis might be related to abnormal peripheral opioid system. To date there is no single antipruritic therapy dedicated specifically to treat itch in psoriasis. Treatment of pruritus in patients with psoriasis should be directed mainly toward the resolution of skin lesions. However, there is an urgent need for the development of specific antipruritic therapy for this group of patients.

OP41

TOPICAL CALCINEURIN INHIBITORS IN ENDOGENOUS ECZEMA AND CANCER ASSOCIATION: A COHORT STUDY

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Topical calcineurin inhibitors (TCIs) have been widely used as a steroid-sparing agent in eczema. However, the long-term cancer risk associated with their use remains unclear. We performed a retrospective cohort study to evaluate the association between TCIs and cancer among patients diagnosed with endogenous eczema at the National Skin Centre, Singapore. Incident cancers were identified from the National Cancer Registry. Data were analyzed using the Cox proportional hazards model to estimate hazard ratios (HR) and 95% confidence intervals (CIs). Adjustment was made for age, gender, ethnicity, cumulative dose of systemic steroids, use of other systemic immunosuppressants and eczema severity. 880 unique cases of cancer developed in 66,176 patients from 2004–2012. The adjusted HRs for overall malignancy were 0.82 (95% CI 0.44–1.39) for tacrolimus-exposed and 1.30 (95% CI 0.59–2.45) for pimecrolimus-exposed. The only significant cancer association observed was lymphoid leukemia among the tacrolimus-exposed:HR 7.58 (95% CI 1.64–25.8). All affected patients had young-onset B-cell leukemia. Subgroup analysis of pediatric patients (≤16 years) showed significant association between tacrolimus use and B-cell leukemia:HR 26.4 (95% CI 4.77–146). Pimecrolimus was not associated with any particular malignancy. Use of topical tacrolimus may possibly be associated with B-cell leukemia in pediatric eczema patients. This apparent association should be further studied.

OP42

THE GERMAN EPIDEMIOLOGY HEMODIALYSIS ITCH STUDY (GEHIS): NEPHROLOGICAL AND LABORATORY PARAMETERS DO NOT EXPLAIN CHRONIC ITCH BUT DIURETIC USE MAY DO

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GEHIS is a representative cross-sectional study with 860 HD patients from a randomly selected cluster-sample showing that chronic itch (CI) affects 25.2% of hemodialysis (HD) patients. We investigated possible associations between CI and etiology of the renal disease, comorbidities, laboratory parameters and medications. Charlson Comorbidity Index showed diabetes mellitus in 38.0% (n=327), congestive heart failure in 24.7% (n=212) and peripheral arterial occlusive disease in 21.2% (n=182) as leading comorbidities in HD patients. Diabetes mellitus was the only comorbidity that was significantly, yet inversely, associated with the occurrence of CI. Except for creatinine, phosphorus and parathormone there were no significant associations between the occurrence and characteristics of CI and any laboratory value. CI was less prevalent in HD patients with secondary glomerulonephritis. Grouping all patients according to their etiology of renal failure did not reveal any significant differences in comorbidities, dialysis characteristics and laboratory parameters. The loop diuretics (furosemide, torasemide) were significantly negatively associated with the occurrence of CI. There were no associations of CI with other medications. It is most likely that a multifactorial origin may explain CI in HD patients. Future research should focus the role of loop diuretics in CI, on a clinical as well as on a molecular level.

OP43

GENERALIZED PRURITUS PROVOKED BY LYSOPHOSPHATIDIC ACID-INDUCED HISTAMINE IN A PATIENT WITH PRIMARY SCLEROSING CHOLANGITIS

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Bile acids and/or endogenous opioid imbalances have been implicated in cholestatic pruritus. We report here a generalized pruritus of a 17-year-old Japanese boy with primary sclerosing cholangitis.

Unexpectedly, skin symptoms well responded to H1R antagonist. We did not observe any significant increase of serum total bile acids and the ratio of beta-endorphin to dynorphin-A. On the other hand, serum histamine level was high; it normalized after improvement of liver function. Serum level of autotaxin, a lysophosphatidic acid (LPA)-synthesizing enzyme, also decreased when liver function was improved. Blood leukocytes produced histamine in response to synthetic LPA *in vitro*, and the histamine release was inhibited by pre-treatment of blood cells with a LPA receptor type 1/3 antagonist. These data suggested that LPA directly stimulated blood basophils and/or cutaneous mast cells to release histamine, leading to generalized pruritus. Although the histamine/LPA/ATX axis cannot be generalized to all the cholestatic patients, the present case may provide a clue for understanding a novel mechanism of pruritus in cholestasis.

OP44

LPA INDUCES ITCH AND PAIN IN HUMANS DEPENDING ON THE MODE OF APPLICATION

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Lysophosphatidic acid (LPA) was recently identified as potential mediator of cholestatic pruritus. LPA induced scratching behavior in mice, but has also been shown to play a role in neuropathic pain. To further elucidate the role of LPA-mediated itch and pain signaling we analyzed the effect of LPA application into human skin by psychophysical examinations. LPA was applied intradermally either by injection or focally by inactive cowhage spicules in healthy volunteers (n=18). Pain and itch intensities were quantified using verbal rating scales. The axon reflex flare reaction was determined by Laser doppler imaging. Additionally electrical hypersensitivity, thermal and mechanical hyperalgesia were tested. Focally applied LPA induced a mild itch sensation, whereas intradermal injection of LPA caused a dose-dependent burning pain. In contrast to histamine LPA induced a mild flare reaction. LPA caused only heat hyperalgesia, but no change in cold, mechanical or electrical sensitivity. These results are in line with the spatial contrast theory in which a focal activation of few sensory neurons with silent surrounding neighboring neurons is perceived as itch whereas a broad neuronal activation results in pain sensation. Currently developed LPA receptor blockers may represent a novel class of drugs for anti-pruritic and analgetic treatment.

OP45

PRURITUS: AN UNDERRECOGNIZED SYMPTOM OF SMALL-FIBER NEUROPATHIES

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Small-fiber neuropathies (SFN) are diseases of small nerve fibers that are characterized by autonomic and sensory symptoms. To evaluate sensory symptoms, especially pruritus, a questionnaire was given to all patients with SFN, confirmed by positive biopsy specimen. In all, 41 patients responded to the questionnaire (71.9% response rate). There were 26 women and 15 men (mean age 61.5 years). Most frequent causes of SFN were Gougerot-Sjogren disease (39.0%), idiopathic (34.1%) and diabetes (14.6%). The most frequent sensory symptoms were burning (77.5%), pain (72.5%), heat sensations (70.2%), and numbness (67.5%). Pruritus was present in 68.3% of patients. It appeared most often in the evening, and was localized to the limbs in a distal-to-proximal gradient, although the back was the most frequent location (64%). At its worst, pruritus was intense (7.4/10), and on average, it was rated as 4.8/10. Exacerbating factors were fatigue, xerosis, sweating, hot temperature, and stress. Cold water was an alleviating factor. 71% of patients scratched their skin "very often" or "often". Scratching was considered as pleasurable or unpleasurable by patients. In conclusion, pruritus occurs frequently in patients with SFN and could be recognized as a possible presenting symptom, especially if there are other sensory or autonomic symptoms

EPIDEMIOLOGY OF ITCH AND PATIENTS' PERSPECTIVES

OP46

PREVALENCE AND RELEVANCE OF PRURITUS IN PREGNANCY

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Introduction: Pregnant women are at greater risk to suffer from chronic pruritus, but data on this symptoms in this group are very limited. Objective: To investigate the prevalence, clinical characteristics and the importance of pruritus in pregnant women. *Methods:* A total of 262 consecutive pregnant women at the 33.0±6.0 week of gestation (WoG) were recruited into this prospective, cross-sectional study. All patient underwent thorough anamnesis and detailed physical examination with the special emphasis on pruritus. Pruritus was assessed according to Visual Analogue Scale (VAS). Quality of life was measured with the Dermatology Life Quality Index (DLQI). *Results:* The point prevalence of itch was 19.8% (n=52), while the whole-pregnancy prevalence was 35.9% (n=94). Further 13 (4.9%) women experienced pruritus during one of the previous pregnancies. By 65.3% and 50.0% pruritic women, respectively, itching was described as annoying and burdensome. Pruritus started at 27.5±7.3 WoG – it was more common among women in third (25.6%) than in second (9.5%) and first trimester (0.8%). The mean VAS was 5.8±2.5 points. The DLQI scoring significantly correlated with VAS (r=0.49, p<0.001). *Conclusions:* About one third of women suffer from pruritus during pregnancy, which for many pregnant women is a very distressing and disturbing symptom.

OP47

ITCH INTENSITY AND UNDERLYING CAUSE OF ITCH REPORTED BY COMMUNITY DERMATOLOGISTS IN THE UNITED STATES

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Background: Chronic pruritus (CP) is a common complaint received by dermatologists. There are few studies on the epidemiology of CP and clinical practices of dermatologists treating this symptom. *Objectives:* We sought to understand the intensity of itch patients reported and the extent to which an underlying cause of itch was diagnosed. *Methods:* 3,577 US dermatologists from an AMA database were invited to participate in an email screener that queried patient load for various dermatological conditions, without revealing pruritus was the focus of the screener. 275 of 291 respondents reported 10 or more CP patients per year. These respondents then participated in an on-line questionnaire containing 55 questions. 212 of 275 respondents completed the survey. *Results:* Surveyed dermatologists reported mean itch intensity of their patients as mild (22%), moderate (38%), severe (27%) and very severe (13%). Physicians were confident (35%) or somewhat confident (26%) that the underlying cause of itch had been identified while reporting that the cause had not been identified in 40% of patients. *Conclusions:* Dermatologists are confident in their diagnosis of an underlying cause of itch in a minority of cases and itch intensity is severe or very severe in 40% of cases.

OP48

CHRONIC ITCH IN HEMODIALYSIS PATIENTS: CUTANEOUS MANIFESTATIONS AND PROVISION OF CARE ACCORDING TO GEHIS (GERMAN EPIDEMIOLOGICAL HEMODIALYSIS-ITCH STUDY)

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GEHIS (German Epidemiological Hemodialysis Itch Study) is a representative cross-sectional study including 860 hemodialysis (HD) patients. 25.1% (n=217) suffered from current chronic itch (CI), 177 out of them received an examination by a dermatologist in order to classify CI according to the classification of the International Forum for the Study of Itch (IFSI) and to document cutaneous manifestations. Severity of CI (visual analogue scale, VAS) and itch-related quality of life (ItchyQoL) were assessed. 89.8% (n=159) showed xerosis cutis which was the most frequent finding. 43.5% suffered from CI without any skin lesions (IFSI II), 37.9% had secondary scratch lesions (IFSI III), 18.6% showed primarily diseased skin (IFSI I). Severity of CI and ItchyQoL showed a significant association only with IFSI III. 22.9% (n=39) had ever consulted a physician/dermatologist for CI, 50% of them corresponded to IFSI III. Only 32.4% (n=77) had ever received any treatment for CI and they suffered from significantly more severe CI (p<0.03). This study shows that almost half of the HD patients with CI present with normal looking skin. This may explain why CI in HD patients is not sufficiently treated and should encourage a better collaboration between nephrologists and dermatologists.

OP49

CHANGES IN UREMIC PRURITUS INCIDENCE AND SEVERITY OVER SIX YEARS IN A HEMODIALYSIS CLINIC

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Using an identical simple questionnaire the present status of uremic itch in all the hemodialysis outpatients of a hemodialysis clinic in Tokyo was investigated in 2008 and 2014. The total of 70 patients in 2008 and 78 patients in 2014 participated in the study. The severity of itch was assessed with verbal rating scale of itch intensity. The incidence of pruritus over the previous week was similar (58.6% in 2008 and 50.0% in 2014, not significant). However, itch intensity showed a remarkable improvement. The percentage of those who rated as 'very severe itch' decreased from 39.0% in 2008 to 10.2% in 2014 (p<0.01). The incidence of severe sleep disturbance due to itch decreased from 12.2% in 2008 to 7.6% in 2014, though the change was not statistically significant. The percentage of those who were satisfied with the treatment increased from 22.6% in 2008 to 68.0% in 2014. The better control of serum phosphorus, vigorous effort of foot care by nursing staff, introduction of a kappa opioid agonist nalfurafine and the support by a dermatologist to use potent topical corticosteroids and to add narrow band ultraviolet B therapy seemed to be the contributing factors for the improvement of patients care.

NEW RECEPTORS OF ITCH

OP50

HTR7 MEDIATES SEROTONERGIC ACUTE AND CHRONIC ITCH

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Chronic itch is a prevalent and debilitating condition for which few effective therapies are available. We harnessed the natural variation across genetically distinct mouse strains to identify transcripts co-regulated with itch behavior. This survey led to the discovery of the serotonin receptor, HTR7, as a key mediator of serotonergic itch. Activation of HTR7 promoted opening of the ion channel TRPA1, which in turn triggered itch behaviors. In addition, acute itch triggered by serotonin or a selective serotonin reuptake inhibitor required both HTR7 and TRPA1. Aberrant serotonin signaling has long been linked to a variety of human chronic itch conditions, including atopic dermatitis. In a mouse model of atopic dermatitis, mice lacking HTR7 or TRPA1 displayed reduced scratching and skin lesion severity. These data highlight a role for HTR7 in acute and chronic itch, and suggest that HTR7 antagonists may be useful for treating a variety of pathological itch conditions.

OP51

CELLULAR AND MOLECULAR SIGNALING OF LYSOPHOSPHATIDIC ACID-INDUCED ITCH SENSATION

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Itch is an unpleasant cutaneous sensation provoking a desire to scratch. Various itch-inducing molecules have been revealed to activate receptors expressed in dorsal root ganglion (DRG) neurons that initiate itch signaling in the periphery and transmit it to the central nervous system. Among them, lysophosphatidic acid (LPA) was found as an itch mediator involved in cholestatic itch, however,

it is still controversial whether LPA is a mediator of itch, pain or both in the periphery. Moreover, the underlying cellular and molecular signaling in DRG neurons induced by LPA is still unknown. In this study, we used a cheek injection method and revealed that LPA induced inch-related behaviors rather than pain-related behaviors, which are dependent on transient receptor potential ankyrin 1 (TRPA1) and vanilloid 1 (TRPV1) both of which are important for itch sensation. Additionally, pharmacological approaches with a calcium imaging method focusing on LPA receptors and intracellular phospholipases expressed in DRG neurons showed that LPA5 receptor and phospholipases D (PLD) play a crucial role in the LPA-induced calcium signaling. Our results suggest that LPA is an itch mediator to induce peripheral itch sensation through the signaling of LPA5, PLD, TRPA1 and TRPV1 in DRG neurons.

OP52

ARE KERATINOCYTES AND SOME ITCH MEDIATORS INVOLVED IN THE NEUROPEPTIDE RELEASE INDUCED BY PACIFIC-CIGUATOXIN-2 IN A SENSORY NEURON-KERATINOCYTE COCULTURE MODEL?

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Ciguatera Fish Poisoning (CFP) is caused by the consumption of fishes contaminated by ciguatoxins (CTXs). One of the most characteristic clinical signs is an intense pruritus which can persist for several weeks and is poorly or not relieved by antihistamine drugs. It is admitted that CTXs bind to Voltage-Gated Sodium Channels but the molecular mechanisms underlying CTX-induced itch remain unclear. Skin cells or skin afferents fibres can release pruritogen substances, such as substance P (SP) and Calcitonin Gene-Related Peptide (CGRP), and express emerging receptors, including some TRP (Transient Receptor Potential) channels and some Protease-Activated Receptors (PARs), that have been shown to mediate or facilitate pruritus. We showed that nanomolar concentrations of Pacific-CTX-2 induce a substantial SP and CGRP release from a co-culture of human keratinocytes and rat DRG neurons. The aim of this study was to dissect the cellular and molecular mechanisms of this effect. In particular, the involvement of keratinocytes, PAR-2 and some TRPs channels were studied using pharmacological tools and calcium imaging experiments. CFP-associated pruritus has never been the subject of any study. This work may not only identify new potential targets for treating ciguatera but is also an original way to better understanding the pathophysiology of itch.

OP53

SUBSTANCE P ACTIVATES MRGPRS TO PROVOKE ITCH

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Introduction: Substance P (SP) is a neuropeptide and key mediator of itch. Neurokinin-1 (NK1) is the classical receptor for SP but NK1 antagonists have limited effectiveness for the treatment of itch. Mrgprs receptors are pivotal for histamine-independent itch. We asked if SP activates Mrgprs and if blocking Mrgprs would prevent SP-induced itch. *Methods:* SP-induced itch was compared between NK1 knockout and Mrgpr knockout mice. The interaction between SP and mouse and human Mrgprs was studied in cultured DRGs from NK1 knockout and wildtype mice and in transfected cells. *Results:* SP-induced itch was normal in NK1 knockout mice but decreased in Mrgpr knockouts. SP activated mouse MrgprA1 and human-MRGPRX2. We identified an inhibitor of these Mrgprs. The inhibitor blocked the activation of NK1 knockout DRGs and itch in wild type mice. The inhibitor also blocked itch induced by classical pruritogens including compound 48/80 and SLIGR. In contrast, NK1 specific antagonists had no significant effect on itch. *Conclusion:* SP is a ligand for hMRGPRX2. HMRGPRX2 is expressed on DRGs and mast cells and transmits itch. The inhibitor we have identified, or a derivative, has the potential to be a treatment for histamine-independent itch and allergic conditions associated with SP.

OP54

EXPRESSION OF OPIOID RECEPTORS IN THE SKIN OF PATIENTS WITH UREMIC PRURITUS

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Uremic pruritus is a common symptom in patients with chronic kidney disease undergoing hemodialysis (HD) treatment. Etiopathogenesis of uremic pruritus is complex and has so far failed to be fully explained. There are some suggestions that peripheral opioid system may contribute to the pathogenesis of pruritus. This study was undertaken to analyze the expression of mu and kappa opioid receptors in the skin of HD patients with and without uremic pruritus. The study included 41 subjects on maintenance HD: 21 with itching and 20 without pruritus. Itch intensity was scored with the visual analogue scale (VAS). The average severity of pruritus was 3.6±3.8 points. The expression of opioid receptors in the skin was studied with immunohistochemistry. The significant (p<0.03) decrease in kappa opioid receptor expression was shown in the skin of pruritic uremic subjects compared to those free from itch (1.1±0.62 and 1.7±0.85, respectively). There was no difference in the expression of mu opioid receptors between studied groups. Moreover, there was a significant negative correlation between intensity of pruritus and expression of kappa opioid receptors (R=–0.48, p<0.001). This study indicates that disturbances in peripheral opioid system may be of importance in the pathogenesis of uremic pruritus.

PRURIGO AND OTHER PRURITIC DISEASES

OP55

PRURIGO NODULARIS: UPDATE ON CLINICS AND TREATMENT

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Prurigo nodularis (PN) is a highly pruritic skin disease associated with dermatological (e.g. atopic dermatitis) and non-dermatologi-

cal comorbidities, including internal, neurological, and psychiatric diseases. Its pathophysiology remains unknown, but peripheral sensitization and dermal neuronal hyperplasia of substance P-positive nerve fibers may be involved. Clinically, a broad range of lesion types are seen, for example, papular, nodular, plaque, ulcerative and umbilicated ulcerated lesions. All PN patients have a high burden and severely reduced quality of life due to visible, consistently bleeding skin lesions and lack of available treatment options. Treatment of PN continues to be challenging. Few randomized controlled trials (RCT) investigating the efficacy of topical pimecrolimus, topical steroids, and certain phototherapies on PN have been carried out, but each different therapy has been evaluated in case series or case reports. Based on our experience, we have developed a treatment ladder for PN comprised of the most effective treatment options. These include pregabalin, gabapentin, naltrexone, and immunosuppressants such as cyclosporine and methotrexate. Recently, RCT's have begun investigating the efficacy of neurokinin 1 (NK1) receptor antagonists and the kappa opioid receptor agonist/μ-opioid receptor antagonist nalbuphine in treating PN.

OP56

ASPIRIN AND LOXOPROFEN RELIEVED PRURITUS IN A PATIENT WITH PRURIGO NODULARIS

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A 56-year-old man presented with numerous pruritic nodules over the trunk and proximal extremities of 3 months duration. Initial treatment with topical corticosteroids and antihistamine had no effect. We started his treatment using an our original therapeutic algorithm for prurigo. Combination of antihistamine, olopatadine and loratadine, and additional roxithromycin slightly relieved his pruritus. Next, pregabalin relieved the itch incompletely. Oral cyclosporine at 2.5 mg/kg a day finally comforted him and prurigo nodules had gradually disappeared. During 6-months observation he repeatedly experienced that both aspirin and loxoprofen, which were taken for his headache and accidental foot injury, obviously reduced the itch for 3–4 hours after taking them.

OP57

PATHOPHYSIOLOGY OF PRURITUS IN PRIMARY LOCALISED CUTANEOUS AMYLOIDOSIS

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Primary localized cutaneous amyloidosis (PLCA) is a chronic pruritic dermatosis which pathophysiology is poorly understood. We aim to investigate if small fibre neuropathy, which comprises of a reduction in intra-epidermal nerve fibres (IENF) and abnormalities in quantitative sensory testing (QST), is present in PLCA. We examined 20 Chinese patients and compared with 20 matched-controls. QST was performed bilaterally on the upper back, lateral forearms and shins to determine the warm detection threshold (WDT) and heat pain threshold (HPT). WDT was significantly higher in PLCA patients at all sites and correlated with itch scores ($r=0.59$, $p<0.01$). Skin biopsies revealed a significantly lower IENF counts in patients when compared to age-, gender-, ethnic-, and site-matched normal skin obtained from previously-stored paraffin-embedded specimens (PGP9.5, tubulin beta-3 and NF200 stains: all $p<0.0001$). Increased expression of the subunits of IL-31 receptor, which is an established neuroimmune link for the generation of T cell-mediated itch, was observed in patients: OSMRβ ($p<0.005$) and IL-31RA ($p<0.001$). Our study indicates the presence of small fibre neuropathy in PLCA. The pathogenesis of itch in PLCA may involve a reduction in IENF and hypersensitivity of the remaining itch-transmitting nerve fibres, which is associated with an increased expression of IL-31 receptors.

OP58

A PROSPECTIVE, LONGITUDINAL STUDY TO COMPARE THE PREVALENCE OF PAIN AND ITCH FOLLOWING HERPES ZOSTER INFECTION AT A TERTIARY CARE CENTRE, EASTERN INDIA, WITH SPECIAL EMPHASIS ON THE DLQI OF PATIENTS

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Introduction: Even after healing of Herpes zoster (HZ), there is distress, traditionally in the form of pain (Zoster associated pain-ZAP). Recently, itching has being reported as an emerging, new symptom. Both conditions adversely affect the patient's Qol. *Aims and Objectives:* 1) To assess the prevalence of itch following HZ infection, and compare it with pain. 2. To compare the DLQI of patients on successive follow-ups. *Materials and Methods:* A prospective longitudinal study was conducted among 91 HZ patients at a tertiary care centre, Eastern India. They were followed up monthly, for 3 consecutive months. *Results and analysis:* Amongst 91 patients, 55 (60.43%) suffered from pain alone, 9 (9.89%) complained of itching alone while 27 (29.67%) suffered from both. Diabetes mellitus (29.27%) and malignancy (44.44%) were the most important co-morbidities, in the two groups respectively. Thoracic dermatomal vesicular lesions were the commonest in both groups. However, pustules were commoner in the patients who presented with pain. DLQI had a significant improvement in both groups ($p<0.001$; Mann Whitney test), 2nd FU onwards. *Conclusion:* Itching is emerging as a new symptom following Herpes zoster infection, so one must be vigilant, to arrive at the proper diagnosis.

OP59

DIRECT TSLP-T CELL INTERACTION IN ATOPIC DERMATITIS

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TSLP is known to interact with skin DCs via TSLP receptor (TSLPR) to promote Th2 differentiation. On the other hand, human T cells in resting state do not show TSLPR expression, and TSLP-T cell interaction has been given less notice. Interestingly, analysis of 51 atopic dermatitis (AD) patients show that CD4+ T cells in PBMCs of these patients show significantly enhanced TSLPR expression ($p<0.005$), and the receptor expression on these cells correlate with disease activity. In vitro research using isolated CD4+ T cells clearly indicate that these TSLPR expres-

sing T cells interact directly with TSLP to promote enhanced IL-4 production compared to CD4+ T cells isolated from psoriasis patients or normal individuals ($p<0.01$). TSLP treated CD4+ T cells also show up-regulated CCR4 expression, and proliferation of IL-4 producing CD4+ T cells is strongly induced compared to IL-2 or IL-4 treated samples ($p<0.05$). Moreover, TSLP treatment also induces the up-regulation of IL-4 receptor, and alternatively, IL-4 treatment induces TSLPR expression on CD4+ T cells from these patients. These observations obtained from experiments using freshly isolated CD4+ T cells from AD patients suggest the possible positive-feedback-loop mechanism between TSLP and IL-4, which may contribute to the persisting Th2 reaction in these patients.

NEURON PROCESSING

OP60

PARABRACHIAL NUCLEUS MEDIATES ITCH-INDUCED SCRATCHING BEHAVIOR

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The molecular mechanisms of itch have been well studied, however, the circuitry mechanisms of itch signal processing still remain unknown. We found that parabrachial nucleus in the brainstem is activated by intradermal injection of pruritogens. We thus determined the functional role of parabrachial nucleus in the itch signal processing. We found that suppression of neural activity of parabrachial nucleus significantly reduced mouse-scratching behavior in response to a variety of pruritogens. Most of the projection neurons in parabrachial nucleus are glutamatergic neurons, which employs vGluT2 to load glutamate into synaptic vesicles. By stereotaxic injection of AAV-Cre virus into parabrachial nucleus of Vglut2f/f mice, we selectively blocked the release of glutamate from parabrachial nucleus as detected by in vitro patch clamp recording. We found that blocking the release of glutamate release of parabrachial nucleus decreased the scratching number in both histamine-dependent and histamine-independent itch models. Surprisingly, the pattern of scratching behavior is also affected as detected by high-resolution scratching behavior recording. Using in vivo extacellular recording, we found that neural activity of neurons in the parabrachial nucleus correlates with mouse scratching behavior. Our study thus demonstrates that parabrachial nucleus plays an essential role in mediating the itch-induced scratching behavior.

OP61

A SPINAL MICROCIRCUIT THAT MEDIATES THE INHIBITION OF ITCH BY COUNTER-STIMULI

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Counterstimulation such as noxious or cool stimuli is known to relieve itch. However, its precise mechanism is still unknown. Recently we have found Bhlhb5-/- mice, which lack a certain population of spinal inhibitory interneurons (B5-I neurons), develop pathological itch. B5-I neurons belong to the population that expresses galanin and/or nNOS. Here we studied itch relief mechanism of nNOS-expressing inhibitory neurons in lamina I using nNOS-creER/Channelrhodopsin mice. We developed a new, semi-intact somatosensory preparation that enables us to record spinal cord neurons in response to pain and/or itch stimulation to the skin. Consistent with our previous report, we find that nNOS-expressing spinal interneurons receive noxious and cool input from the skin. In addition, we observed that a subset of lamina I cell responded to itch stimulation such as serotonin or cowhage spicules. Optogenetic activation of nNOS-expressing spinal interneurons induced IPSCs in a subset of lamina I neurons. Moreover, action potentials that were evoked by topical application of serotonin were shut down by optogenetic activation of nNOS-expressing interneurons. These data indicate that activation of nNOS inhibitory interneurons by noxious stimuli suppresses the activity of itch-mediating lamina I neurons.

OP62

IN VIVO WHOLE-CELL PATCH-CLAMP ANALYSIS OF DRG NEURONAL EXCITATION AND SUPPRESSION BY CHLOROQUINE IN ADULT RATS

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Dorsal root ganglion (DRG) neurons are functionally heterogeneous. Chloroquine (CQ) is an antimalarial drug that is believed to excite TRPA1 by activating MrgA3 in the subsets of nociceptive DRG neurons to induce an itching sensation. Here we used an original method for *in vivo* patch-clamp recording to enable an integrated analysis of the diverse properties of DRG neurons in rats and investigated the effects of CQ on DRG neuronal excitability. DRG neurons that innervate the skin were screened according to their axonal conduction velocity (C-type and Aδ-type), action potential duration, and current expression profiles (Ih, IA, and T-Ca) and were classified into classes I–V. The intradermal injection of 1 mM CQ into the receptive field evoked discharges in some class I DRG neurons characterized by C-type, high-threshold mechanosensitivity, long action potential, and small Ih or Class II DRG neurons characterized by C-type, moderate-threshold mechanosensitivity, shorter action potential, and IA. An additional injection of 10 mM CQ interrupted the 1 mM CQ-induced discharge. These results suggest that CQ paradoxically exerts excitatory and suppressive actions in itch-mediating DRG neurons by exciting TRPA1 and modulating voltage-dependent sodium and potassium channels.

OP63

PERIPHERAL NEURONAL MECHANISMS OF ITCH IN PRIMATE

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Over the last decade, considerable progress has been made in unraveling the peripheral neuronal mechanisms of itch. Psychophysical experiments in human and electrophysiological recordings in primate have revealed that histaminergic and non-histaminergic itch is mediated through separate afferent pathways, and that both, small myelinated and unmyelinated nociceptive afferents, can mediate itch sensation. Experimental evidence further suggests

that different pruritogens preferentially activate different classes of nociceptive afferents. In this presentation, a summary of the results from studies in human and nonhuman primates will be presented, which, taken together, indicate that a single, labeled line for itch is unlikely to mediate itch sensation in primates.

MENTAL ITCH AND QUALITY OF LIFE

OP64

PSYCHOGENIC ITCH: ASPECTS OF CLINICAL SYSTEMATICS, COMPLEX THERAPY AND PROPHYLAXIS

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Actuality of itch phenomena is determined by its high prevalence, problems of diagnostics, not clarified mechanisms of pathogenesis and limited therapeutic methods. The aim of our work was to determine systematics, to study clinical picture, to improve complex therapy of psychogenic itch based on complex clinical (dermatologic, psychiatric, psychological) examination. In the period 2009–2013 60 patients (54.28±15.79 years) with itch duration about 5 years were examined by psychodermatological group including Visual analog scale (VAS), Eppendorf index, Lyfe Style Index, Mini-Mult index, Hospital Anxiety and Depression Score. As a result of the study there were 3 groups of patients: the 1st group of patients with psychogenic itch (n=28), the 2nd group of patients (n=18) with amplified itch that didn't correlate with severity of skin lesions in skin diseases and the 3d group with itch by neurotic excoriations (n=14). According to VAS in 46.7% (n=28) itch intensity was high – more than 7 points – and in 43.4% (n=26) medium – 4–6 points. The relationship of psychotraumatic factor in these 3 groups was statistically significant (p=0.038). Patients with psychogenic itch had somatoform disorders in 41.3%. Complex treatment with dermatological and psychotropic drugs allows achieving clinical efficiency in 58.4% in treatment of psychogenic itch.

OP65

DECREASED QUALITY OF LIFE IN PATIENTS WITH MOOD DISTURBANCES AND CHRONIC ITCH

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Background: Psychological variables, such as stress, can worsen the severity and perception of itch. This study considers the relationship between mood disturbances and the impact of itch on quality of life (QoL). *Methods:* Patients were recruited from an Itch Clinic and given ItchyQoL, a self-reported QoL scale with 27 questions rated from 1 to 5. Average scores were calculated. A chart review identified patients who reported mood disturbances, defined as anxiety or depression. *Results:* Of the 109 subjects, 39% of patients reported mood disturbances. Patients with mood disturbances had higher baseline ItchyQoL scores (mean 3.47 vs 2.9, respectively, p= 0.001) and higher emotional subscale scores (mean 3.56 vs 2.94, respectively, p=0.002) than their counterparts. Patients with mood disturbances had an average decrease of 0.63 points on subsequent ItchyQoLs (n=19) compared to their baselines for both overall and emotional scores (p= 0.009 and 0.002). This was not significant for patients without emotional symptoms. *Conclusion:* These results demonstrate an association between mood disturbances and the QoL impact of chronic itch. However, the directionality of this relationship is unclear. The improvement in subsequent ItchyQol scores suggests possible emotional benefits to Itch Clinics.

OP66

IS UREMIC PRURITUS STILL AN IMPORTANT CLINICAL PROBLEM IN MAINTENANCE HEMODIALYSIS PATIENTS?

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The aim of this study was to evaluate the frequency and severity of uremic pruritus in hemodialysis patients and to correlate its presence and intensity with the quality of life and sleep problems. A total of 171 patients participated in the study. The intensity of pruritus was assessed with visual analog scale (VAS) and the 4-item itch questionnaire; quality of life with Dermatology Life Quality Index (DLQI) and sleeping problems with Athens Insomnia Scale (AIS). 52.6% of patients had uremic pruritus in the past. Moreover, 46.2% were affected by itch during last three days. The mean VAS was 4.1±2.0 points. 52.6% of patients reported itch as mild, 38.2% as moderate, 7.9% as severe and 1.3% as very severe. 50% of individuals with pruritus showed impaired skin-related quality of life. Uremic pruritus intensity assessed with VAS correlated with the quality of life (r=0.25, p=0.05). Moreover, the intensity of itch assessed with the 4-item questionnaire correlated with sleep problems (r= 0.27, p=0.017). Uremic pruritus seems to be still a common phenomenon in hemodialysis patients. However, its intensity in the majority of subjects is mild to moderate. The severity of itch shows a weak relationship between the quality of life and sleep problems

OP67

CHRONIC ITCH IN HEMODIALYSIS PATIENTS: PAIN IS AN ADDITIONAL BURDEN REDUCING HEALTH-RELATED QUALITY OF LIFE (HRQOL)

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GEHIS (German Epidemiological Hemodialysis Itch Study) is a representative cross-sectional observational study including 860 hemodialysis (HD) patients. It showed that the point prevalence of chronic itch (CI) in HD equals 25.2%. GEHIS also demonstrated that the emotional well-being (Hospital Anxiety and Depression Scale, HADS) and health-related quality of life (HRQOL) including Short Form Health Survey (SF12) were significantly more impaired in HD patients with CI and itch specific QOL (ItchyQoL) was significantly associated with the severity of CI. As pain is also a major health problem in HD patients we investigated its role in patients with and without CI. 85.5% (n=735) of all HD patients

were affected by pain (muscle, chest, cramps). HD patients with CI had significantly more pain and complained of pain impairing daily activities significantly more frequent than those without CI. Sleep quality (but not duration) was also significantly impaired when CI patients additionally suffered from pain. There was no significant difference regarding comorbidities in CI patients with and without pain. The current analyses demonstrate the impact of pain on HRQOL in HD patients with CI. The care of HD patients should not only consider CI and pain but especially respect those complaining both sensations simultaneously.

OP68

RACIAL DISPARITIES IN PRURITUS QUALITY OF LIFE AND RESOURCE UTILIZATION

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Racial disparities in chronic pruritus have been reported previously. We investigated potential racial differences in quality of life (QoL) impact and resource utilization using data from our US Veterans Pruritus Study. Race was defined as self-reported "White", "Black/African American" or "Other". ItchyQoL is a 22-item self-reported survey on itch-specific QoL impact for the preceding week. Medical resource utilization included physicians' visits, medications, alternative therapies, and loss of time or income due to symptoms, all from the preceding 3 months. Of the 405 patients with chronic pruritus, Blacks (18%) had a significantly higher QoL impact, even after adjusting for sociodemographic variables and itch severity. Individual ItchyQoL items reveal sources of these differences (all $p<0.05$) to be the use of special soaps and clothes, scars, burning, and multiple emotional items. Blacks were also significantly more likely to visit their primary care provider for pruritus ($p=0.03$), yet had similar numbers of specialty care visits. Additionally, blacks more frequently used extra help for daily tasks ($p=0.05$). The data indicate a racial disparity in pruritus for both QoL impact and resource utilization. These findings merit further exploration into explanations such as access, communication, trust of the medical system, and biological differences.

BRAIN IMAGING

OP69

ARE THERE DIFFERENT CEREBRAL NETWORKS FOR ITCH AND BURNING INDUCED BY IRRITANT SUBSTANCES?

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Inactivated cowhage spicules coated with histamine and capsaicin were inserted in the skin of 15 healthy subjects in a double blind fMRI study. Each spicule application was followed by an fMRI measurement while the subjects were repeatedly scratched proximal to the spicule application site. High itch periods (Hi) immediately before scratching were followed by low itch during and immediately after scratching. Sensory qualities and the relief of itch by scratching were rated. Both agents induced mixed itching and burning sensations. Capsaicin ($p<0.002$) induced significantly more burning than histamine. Scratching had a significantly stronger itch alleviating effect after histamine ($p<0.0014$) than after capsaicin. Independent of the spicule type similar cerebral BOLD clusters were activated during Hi and scratching. Differences between agents were revealed by contrast analyses. Itch relief by scratching following histamine was associated with negative BOLD effects in several areas, most prominent in the posterior cingulate cortex, while it was absent following capsaicin. The effect was contrary only in BA7. During Hi burning after capsaicin induced activation in the right BA40 and deactivation in the left BA9. Contrast analyses revealed differential processing related to the burning component during the Hi period and related to the itch relief by scratching.

OP70

EFFECTIVE ULTRASTRUCTURE NEUROIMAGING OF ITCH

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Gastrin-releasing peptide (GRP) receptor has been identified as an itch mediator in the somatosensory system. We focused on the ligand of GRP receptor, GRP as a molecular marker of itch neural circuit. We demonstrated that GRP was expressed in the small-sized primary afferents, and central fibers terminated the superficial layers of spinal dorsal horn and spinal trigeminal nucleus caudalis in rats. These findings suggested that GRP is an important neuropeptide for itch transmission not only in the spinal somatosensory system but also in the trigeminal somatosensory system. Furthermore, we used high-voltage electron microscopy (HVEM) and 3-dimentional scanning electron microscopy (3D SEM) combined with immunohistochemistry to analyze the 3D ultrastructure of the itch-mediating synaptic formation in the spinal dorsal horn. HVEM at an ultrahigh accelerating voltage (1,000 kV) showed that GRP-containing terminals formed a series of varicosities. 3D-SEM analysis showed that GRP terminals connected many postsynaptic components than expected. The combination of HVEM and 3D SEM with immunohistochemistry effectively reconstructs the 3D ultrastructure of both itch-mediating synaptic connectivity and chemical neuroanatomy. These results suggested that itch transmission was complex control in the spinal dorsal horn.

OP71

BRAIN PROCESSING OF CONTAGIOUS ITCH IN PATIENTS WITH ATOPIC DERMATITIS AND HEALTHY CONTROLS

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Background: Itch and scratching evoked by visual itch stimuli coined "Contagious Itch" are more pronounced in patients with atopic dermatitis (AD). The brain mechanisms behind this robust phenomena in atopics have not been investigated yet. *Methods:* 11 AD patients and 8 healthy controls susceptible to visual itch cues underwent fMRI scans. They were shown an itch inducing experimental video (EV) and a non-itch inducing control video (CV) in- and outside the scanner. Perfusion based brain activity was measured using arterial spin labeling functional MRI. *Results:* In AD patients CI led to a significant increase in brain activity in the supplementary motor area (SMA; threshold: $p<0.001$; cluster size > 20), while in healthy controls no significant increase in brain activity was observed. In both groups, CI led to a significant increase in itch perception and scratching ($p<0.05$). *Conclusion:* This study demonstrated that the CI phenomena in atopics led to an increase in activation of the SMA, a region that is associated with motor planning and known to be associated with the desire to scratch.

OP72

IN VIVO IMAGING REVEALS THAT NEURAL RECRUITMENT PRECEDES THE INFLAMMATORY INFILTRATE IN A MOUSE MODEL OF ATOPIC DERMATITIS

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Atopic dermatitis is a common cutaneous disorder characterized by severe itch, chronic inflammation and increased nerve fiber density. It has been assumed that the neural changes are in response to ongoing inflammation. We used *in vivo* imaging of fluorescently labeled peripheral sensory nerves over time during epicutaneous sensitization to ovalbumin in an allergic mouse model of atopic dermatitis. Visualization of the same cutaneous nerve branches and blood vessels sequentially over months revealed that peripheral sensory nerves begin to pathfind within 48 hours of antigen exposure and results in higher innervation density and arbor complexity of neuropeptidergic fibers in the skin within days. Neural sprouting preceded changes in vascularization, vascular permeability, and immune infiltration. Blocking neural activation during periods of sensitization prevented ovalbumin-induced changes in neural recruitment and pattern reorganization as well as subsequent inflammatory infiltrate, scratching behavior. These data implicate different roles for recently identified itch molecules in modulating various steps in the inflammatory response. Thus, in contrast to the traditional view that neural changes are reactive to inflammation and scratching, our data suggest that allergic stimulation in a chronic eczema model actually requires neural recruitment and activation for the elaboration and maintenance of the inflammatory cascade.

FUTURE PERSPECTIVE

OP73

FUTURE PERSPECTIVES ON BASIC RESEARCH OF ITCH

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Since IFSI was founded (2005), huge strides have been made in understanding itch mechanisms. Separate pathways signal histaminergic and non-histaminergic itch. Itch transduction involves novel Mas-related G-protein-coupled receptors, protease-activated receptors, cytokines and many others, and downstream activation of TRP and voltage-sensitive sodium channels. Novel behavioral models distinguish among itch, pain, alloknesis and allodynia. Localized skin stimulation evokes both itch and pain, and pruritogen-sensitive peripheral and central neurons respond to algogens, necessitating new theories to explain itch and pain discrimination. Spinal itch-signaling circuitry involves brain natriuretic peptide, glutamate, gastrin releasing peptide and substance P. Disruption of nociceptor input or spinal itch-inhibitory interneurons results in hyperknesis which can be rescued by transplantation of GABAergic neurons. These findings foreshadow many new therapeutic targets and strategies to relieve itch. Nevertheless, many gaps remain. Animal models of chronic itch must be exploited to pinpoint pathophysiological changes in the itch-signaling pathway. Imaging studies have revealed itch-related brain areas, but little is known about the circuitry and neurophysiology of supraspinal itch coding. Itch is affected by many genetic (e.g., sex), physical (e.g., scratching) and psychological factors (e.g., stress), suggesting critical roles for segmental and descending itch-modulatory circuits which need elucidation as future targets for developing antipruritic therapies.

OP74

FUTURE PERSPECTIVES IN TREATMENT OF ITCH

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Over the past decade our understanding of the mechanisms of itch has been revolutionized in particular in the neural system. Subpopulations of specific itch receptors and central neurons have been discovered mainly in animal models. We now better understand that there are different phenotypes of chronic itch. We are entering an exciting era of new drug developments and phase 2–3 trials are already conducted that target itch both in the periphery and in the central neural system that will eventually enter the market. These include drugs that target the neural system such as kappa and mu antagonists and Neurokinin 1 inhibitors as well as drugs that target the immune system and inflammatory itchy cytokines such as IL4 and IL13 inhibitors and interleukin 31. There will be no quick fix treatment for all types of chronic itch. Managing the complexities, challenges and costs of chronic itch will require a comprehensive approach that includes topical and multiple oral itch antagonists.

SPONSORED SEMINARS (SS1–SS6)

SS1

LONG-TERM TOPICAL STEROID THERAPY CAN BE A PROBABLE CAUSE FOR PRURITUS

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Topical steroids are the first-line therapy for the treatment of chronic dermatitis such as atopic dermatitis and allergic contact dermatitis (ACD). Despite its irreplaceable role in therapy, it was reported that topical steroid phobia is frequent in patients with atopic dermatitis, and is significantly correlated with non-adherence to treatment. Insufficient effect of topical steroid is caused by the mistaken information of the side-effects, resulting in prolonged treatment period. Therefore, better understanding of the side-effects of topical steroids is important for adherence to treatment and getting the maximum benefit of the drug. We have reported that the long-term use of topical steroids worsens the pruritic response in spite of its strong anti-inflammatory effect in ACD mice. We also revealed that this long-term topical steroid-induced pruritus was not influenced by the difference in potency of topical steroids and by the strain of mice. The decreased level of prostaglandin (PG) D_2, a well-known endogenous anti-pruritic agent, caused by topical steroids application might be involved in worsening the pruritic reaction. We believe that stimulation of PGD_2 receptor (DP1) by DP1 agonists could be useful for preventing topical steroid-induced pruritus.

SS2

SCRATCHING BEHAVIOR INDUCED BY CENTRALLY ACTING SUBSTANCES IN ATOPIC DERMATITIS MODEL MICE: A CLUE TO UNDERSTANDING SUPRASPINAL ITCH MECHANISMS IN ATOPIC DERMATITIS

Masanori Fujii

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Over the last decade, dramatic progress has been made in understanding peripheral and spinal mechanisms of itch. On the other hand, except for opioids, little is yet known about the molecules that mediate and regulate itch in the supraspinal central nervous system (CNS). We here present novel findings from a unique animal model for atopic dermatitis (AD). HR-1 hairless mice fed a special diet developed AD-like pruritic skin inflammation. In this AD model, itch-related scratching behavior was markedly enhanced by systemic administration of certain CNS depressant drugs (e.g., ethanol and barbiturates, but neither benzodiazepines nor muscimol). Barbiturates enhanced scratching when administered intracisternally but neither intrathecally nor intradermally, suggesting that a supraspinal mechanism is involved in such scratching response. Barbiturate-induced increase in scratching was observed in another AD model, NC/Nga mice, but not in histamine-injected normal mice, suggesting some neural changes in the CNS in mice suffering from chronic AD. Furthermore, we have recently found that allopregnanolone, which is a neurosteroid produced in the brain and has similar actions to ethanol and barbiturates, may participate as an endogenous itch mediator in AD conditions. Thus, our findings open new avenues for investigating the supraspinal itch mechanisms in chronic diseases especially AD.

SS3

ITCH AND THE BRAIN

Yozo Ishiuji

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Itch is defined as an unpleasant sensation which provokes the desire to scratch. Itch has the multidimensional aspects such as the sensory, emotional, attention-dependent, cognitive-evaluative and motivational factors. The brain is the final terminal to receive the itch related signals from the body. It plays an important role in perceiving and modulating the itch sensation. Thus, to understand the cerebral mechanism of itch perception is important for advancing our understanding on the pathophysiology of itch. Functional neuroimaging is the emerging technique such as positron emission tomography (PET) and functional resonance imaging (MRI) to measure the brain activities to understand the relationship between itch and certain brain areas. Using these techniques, it has been demonstrated that the itch brain network contains the pre-motor and supplementary motor area, thalamus, cingulate, insular, inferior parietal, and prefrontal cortices in the healthy subjects. In addition, the brain processing of itch was also reported in the several chronic pruritic diseases such as the atopic dermatitis and the end stage renal failure. Moreover, the brain imaging studies were reported not only in the humans but also in the animals. This lecture summarizes the current studies investigating the relationship between itch and the brain.

SS4

NEW THERAPEUTIC TOOL FOR ITCH – USEFULNESS OF EXCIMER LAMP IN THE TREATMENT OF INTRACTABLE ITCH IN ATOPIC DERMATITIS

Kenji Takamori, Atsuko Kamo, Utako Kimura, Yayoi Kamata, Mitsutoshi Tominaga

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Epidermal hyperinnervation is related to the induction of intractable itch in dry skin showing diseases such as atopic dermatitis (AD). Epidermal hyperinnavation is regulated by axonal guidance molecule (NGF, Semaphorin3A etc.). The density of epidermal nerve fiber is decreased by irradiation with PUVA, NB-UVB and the excimer lamp, which particularly had a strong inhibitory effect on intraepidermal nerve growth and antiprurutic effect. The action mechanisms of excimer lamp on epidermal nerve fibers was different from other UV-based therapies. Irradiation of PUVA and NB-UVB showed down-expression of NGF and up-expression of Semaphorin3A. The excimer lamp, however, had no change in epidermal expression of axonal guidance molecules. This may be explained by our recent finding that excimer lamp irradiation directly induce nerve degeneration in the epidermis. In this seminar, I would like to report the usefulness of excimer lamp in the treatment of intractable itch in AD.

SS5

EVALUATION OF ITCH BY *IN VIVO* PATCH CLAMP METHOD

Daisuke Uta

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The *in vivo* patch-clamp recording technique allows us to clarify the synaptic responses evoked by the various known natural stimuli applied to the skin or other parts and makes it possible to interpret with more certainty the behavioral changes by synaptic plasticity observed at the single cell level. In this session, I'd like to introduce the study of itch by *in vivo* patch clamp method. 5-hydroxytryptamine (5-HT) is often used as a pruritic agent in rodents. However, the mechanism for pruritic synaptic transmission in the central nervous system remains elusive. The present study was designed to analyze pruritic synaptic responses evoked by cutaneous 5-HT stimulation in spinal dorsal horn neurons of adult rats. Behavioral responses to the 5-HT application were also studied. Topical application of 5-HT to the skin provokes scratching. Under voltage-clamp conditions, application of 5-HT to the skin increased the frequency of the large amplitudes of spontaneous excitatory postsynaptic currents (EPSCs). The large amplitudes of spontaneous EPSCs elicited by cutaneous serotonin stimulation were blocked by either CNQX or TTX applied to the surface of the spinal cord. These observations suggest that a subpopulation of superficial spinal dorsal horn neurons convey pruritic excitatory information to provoke scratching behaviors.

SS6

NEW THERAPIES FOR CONTROLLING ATOPIC ITCH

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Chronic itch in atopic dermatitis markedly deteriorates quality of life of affected individuals. Sleep disturbance and impaired productivity in work due to chronic itch impose a socioeconomic burden. Conventional therapies for atopic dermatitis are capable of reducing atopic itch. However, the majority of patients are not satisfied with the anti-pruritic capacity of conventional treatments. In this talk, we will summarize recent progress in itch signaling in skin, dorsal root ganglion and spinal cord. New therapies for controlling atopic itch will also be discussed.

POSTER ABSTRACTS (PP1–PP35)

BASIC RESEARCH TRACK – ANIMAL MODEL

PP1

ITCH-RELATED BITING BEHAVIOR AND NEURONAL RESPONSIVENESS INDUCED BY INTRADERMAL INJECTION OF PRURITOGENS IN HAIRLESS MICE

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Hairless mice (HR-1) are useful to investigate the effects of topical drugs for various dermatological diseases such as atopic dermatitis and herpes simplex virus infection accompanied by itch and pain. We aimed to clarify the characteristics of itch-related behavioral and neuronal responses to pruritogens in HR-1 mice. Histamine (5–5,000 nmol), serotonin (5-HT, 10–300 nmol) and a PAR-2 agonist (SLIGRL-NH2, 10–300 μg) were injected intradermally as a purtitogen into the hindpaw in HR-1 and ICR mice, and biting behavior and spinal neuronal response were measured for 30 minutes. Biting behaviors were dose-dependently observed after 5-HT and SLIGRL-NH2 but not histamine injections in HR-1 mice. The 5-HT and SLIGRL-NH2-induced biting behaviors were more prominent in HR-1 mice than ICR mice. An excitation of spinal dorsal horn neurons were evoked by the 5-HT and SLIGRL-NH2 injections in HR-1 mice, and the frequency of action potentials were also dose-dependently increased. There was a positive correlation between the duration of biting behavior and the frequency of action potentials. These results indicate that the present recordings of itch-related behavioral and neuronal responses elicited in HR-1 mice enable us to study detailed mechanisms for topical antipruritic drug action on histamine-independent itch.

PP2

[LEU11]-HK-1-DERIVED PEPTIDES WITH D-TRP PROLONG ANTIPRURICEPTIVE EFFECTS IN RATS

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Hemokinin-1 (HK-1) is a mammalian tachykinin peptide consisting of 11 amino acids. Recently, it was demonstrated that the previous treatment with [Leu11]-HK-1, in which Met at the C-terminal of HK-1 was replaced by Leu, reduced scratching induced by intrathecal injection of HK-1. Additionally, the pretreatment with [Leu11]-HK-1 attenuated the induction of scratching behavior by pruritogens, suggesting that [Leu11]-HK-1 may have an inhibitory effect on itch processing. Furthermore, it is believed that replacement of amino acids by D-tryptophan (D-Trp), prolongs the effective period. Therefore, to clarify the effective period of [Leu11]-HK-1-derived peptides, the effect of previous treatment with [D-Trp7]-[Leu11]-HK-1, [D-Trp9]-[Leu11]-HK-1 and [D-Trp7,9]-[Leu11]-HK-1 on the induction of scratching behavior by the intrathecal injection of HK-1 and by the intradermal administration of chloroquine and histamine was evaluated. The induction of scratching by intrathecal injection of HK-1 was significantly suppressed until 24 hours after pretreatment with [D-Trp7]-[Leu11]-HK-1 and [D-Trp9]-[Leu11]-HK-1 and 4 hours after [D-Trp7,9]-[Leu11]-HK-1 treatment. On the other hand, intrathecal administration of [D-Trp7,9]-[Leu11]-HK-1 and [D-Trp9]-[Leu11]-HK-1 similarly inhibited the induction of scratching behavior by intradermal injection of a pruritogen, chloroquine and histamine. Taken together, these results suggest that the antipruriceptive effects of [Leu11]-HK-1-derived peptides replaced by D-Trp may be unrelated to the number of D-Trp.

BASIC RESEARCH TRACK – RECEPTORS AND CHANNELS

PP3

STIMULUS-RESPONSE EVALUATION OF THE ANTIPRURITIC EFFECT OF HOMOTOPIC, MONOPHASIC COLD AND TRP-AGONIST COUNTER-STIMULATION ON HISTAMINE-INDUCED ITCH IN HEALTHY VOLUNTEERS

Hjalte H. Andersen[1], Amalie Randers[1], Amalie H. Simoni[1], Anne Jerwiarz[1], Camilla Melholt[1], Jacob B. Pedersen[1], Sigurd D. Hilborg[1], Jesper Elberling[2], Lars Arendt-Nielsen[1]

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The alleviating effect of cold on itch is a common clinical observation. Contradictory results of the antipruritic effect of biphasic cold-modulation exist. We evaluated the counter-stimulatory efficacy of 3-min monophasic cold-stimulation and the effect of pretreatment with topical TRPA1- and TRPM8-agonists. In a two-session, randomized, single-blinded study in 13 volunteers (age: 22.8±3) superficial skin-puncture through a 1% histamine droplet was performed 12 times at their volar forearms. Thermal stimulation was performed 2 minutes after histamine application (3×3cm ATS-probe, Medoc). Applied temperatures were: 4, 12, 22, 28, 32 and 37°C. Chemical counter-stimulation was conducted with 40% l-menthol and 10% trans-cinnamaldehyde and compared to the effects of 5% topical doxepin. Cold detection and pain thresholds were assessed. Outcome measures were itch intensity (VAS 0–10), wheal-size and flare-response. Cold-stimulation alleviated histamine-induced itch in a stimulus-intensity-dependent manner with the temperatures; 4, 12 and 22°C having a significant inhibitory effect, $p<0.05$, compared to 32°C. L-menthol, CA and doxepin reduced itch intensity but trans-cinnamaldehyde also gave rise to pain (VAS 1.6±0.47). Homotopic cold- or cold-like-stimulations in the lower innocuous or noxious range has an inhibitory effect on histaminergic itch. Selective and potent agonists of receptors conveying innocuous cold could be of potential therapeutic value as antipruritics.

PP4

ORPHAN RECEPTOR GPR83 MEDIATES PRURICEPTIVE PROCESSING IN THE SPINAL CORD

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We previously reported that Hemokinin-1(HK-1), a member of tachykinin peptide family including substance P (SP), may have a role of itch transduction in the spinal cord. HK-1-preferred receptor may play a role in itch processing receptor, however, it was not identified yet. We focused on G-protein coupled receptor (GPR) 83 as a candidate of HK-1-preferred receptor based on the homology with NK1R. SP- or HK-1-induced behavior was assessed for elucidation, following intrathecal administration of siRNAs against GPR83 and NK1R. NK1R knockdown attenuated the induction of scratching behavior by SP, but not HK-1 administration into spinal cord, while GPR83 knockdown resulted in decrease of scratching behavior induced by HK-1, but not SP administration. In GPR83 knockdown animal, histamine and serotonin-induced scratching behavior was considerably reduced. In contrast there was little effect of the pretreatment with NK1R siRNA. On the other hand, formalin-induced pain behavior was significantly reduced only by the treatment with NK1RsiRNA. Taken together, these results indicate that GPR83 is a novel receptor involved in the itch transmission system in the spinal cord.

PP5

A NEURONAL BRAKE ON ITCH THROUGH METABOTROPIC GLUTAMATE RECEPTOR ACTIVATION

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Aim: The aim of this study was to identify the possible involvement of inhibitory G-protein coupled metabotropic glutamate receptors (mGluRs) in itch regulation. *Methods:* Itch behavior was assessed in mice injected with an mGluR agonist prior to i.d. injection of several histaminergic and non-histaminergic itch inducing agents. To confirm the inhibitory effect of activation of the mGluR on histamine activated peripheral neurons, calcium imaging was performed in dorsal root ganglia culture cells. *Results:* mGluR agonist treatment reduced itch behavior provoked by histamine, 48/80 and α-methyl serotonin. Histamine and α-methyl serotonin are both associated with the activation of the intracellular enzyme PLCß3 which we could confirm was co-expressed with the mGluR as well as Hrh1, indicating that the mGluR regulates histaminergic and PLCß3-associated itch. This inhibitory effect was functionally confirmed on a neuronal level, where the mGluR agonist strongly modulated histamine calcium evoked responses. *Conclusion:* Here we show that peripheral histamine sensing neurons that express mGluR regulate itch through an inhibitory effect. This finding raises a potential alternative to treat itch in its chronic states, where a down-regulation of itch-related neuronal activity would be achieved through mGluR activation.

PP6

CHLOROQUINE-INDUCED SCRATCHING IS MEDIATED BY NO/cGMP PATHWAY IN MICE

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Chloroquine (CQ) is a 4-aminoquinoline drug has long been used in treatment and prevention of malaria. Generalized pruritus as its side effect contributes to failures of treatment, and consequently developing of plasmodium falciparum chloroquine resistant strains. It is proposed that administration of CQ is correlated with increased nitric oxide (NO) production. Nitric oxide involved in some pruritic disorders like atopic dermatitis and psoriasis and scratching behavior evoked by pruritogens like substance P .So we aimed to investigate the involvement of NO/cGMP pathway in CQ-induced scratching in mice. Scratching behaviors was recorded by a camera after intradermal injection of CQ in the shaved rostral back of the mice. Results obtained showed that CQ elicited scratching in a dose-dependent manner with peak effective dose 400 µg/site. Injection of non-specific NOS inhibitor, N-nitro-L-arginine methyl ester or neuronal NOS selective inhibitor, 7-Nitroindazole reduced CQ-induced scratching significantly. In other hand administration of aminoguanidine as inducible NOS inhibitor has not inhibitory effect on this behavior. Also injection of L-arginine as a precursor of NO significantly increased this response. Conversely accumulation of cGMP by sildenafil as a selective phosphodiesterase type 5 inhibitor potentiated the scratching behavior. This study showed that CQ-induced scratching is mediated by NO/cGMP pathway.

PP7

TOPICAL APPLICATION OF DP1 AGONIST EFFECTIVELY PREVENTS PRURITUS INDUCED BY LONG-TERM TREATMENT OF GLUCOCORTICOIDS IN ALLERGIC CONTACT DERMATITIS MICE

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Topical glucocorticoids (GCs) are the first-line therapy for chronic dermatitis. We previously reported that long-term topical GCs exacerbated pruritus in allergic contact dermatitis (ACD) mice. In the present study, we investigated involvement of prostaglandin (PG) D2 and effectiveness of a DP1 agonist in this pruritus model. Chronic ACD was induced in mice by repeated application of TNCB, and the mice were treated with GC topically for 2 to 5 weeks after the elicitation of ACD. Topical betamethasone valerate (BMV), dexamethasone and prednisolone exacerbated the pruritus of ACD mice irrespectively of their potencies. All GCs reduced mRNA expression of hematopoietic PGD2 synthase in the lesional mouse skin. These GCs suppressed the release of PGD2 from RBL-2H3 mast cells. Topical BW245C, an agonist of PGD2 receptor (DP1), completely suppressed the augmentation

of the scratching behavior induced by topical BMV *in vivo*. These results suggested that the level of PGD2 was decreased in the skin by topical GCs, and then degranulation of the mast cells was accelerated via reduction of DP1 stimuli. Therefore, the topical DP1 agonist would be useful to prevent the augmentation of pruritus in case of long-term topical GCs therapy.

PP8

SPINAL PI3K-GAMMA ACTIVATION MEDIATES GRPR-RELATED ITCHING TRANSMISSION IN MICE

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Gastrin-releasing peptide (GRP) and its receptor (GRPR) are important components of the itch pathway. Signaling pathways downstream of GRPR activation are not clear. We used several approaches to further assess GRPR localization and investigate the related downstream signaling pathways. Functional GRPR is likely expressed by naive DRG sensory neurons since GRP induces calcium flux in small capsaicin-sensitive neurons. Expression profiling reveals that PI3K-gamma is downstream of GRP/GRPR, as observed by GRP-induced Akt phosphorylation in GRPR-transfected cells and *ex vivo* naive mouse spinal cords. Intrathecal GRP administration caused intense scratching behavior, an effect inhibited by pharmacological blockade of GRPR. We assessed whether the GRP/GRPR is involved in chronic itch using the dry skin model and found that a GRPR antagonist reduced itching. The activation of PI3Kg was demonstrated in both itching models, an effect prevented by GRPR blockade. These findings suggest that PI3K-gamma is downstream of GRPR activity. A PI3K-gamma inhibitor reversed both GRP- and dry skin-induced itch in a concentration-dependent manner. Together, these results indicate that GRPR is expressed by DRG sensory neurons and mediate itch via the PI3K-gamma/Akt pathway.

PP9

INVESTIGATION OF ANTIPRURITIC EFFECT MEDIATED VIA ACTIVATION OF NICOTINIC ACETYLCHOLINE RECEPTOR IN THE CENTRAL NERVOUS SYSTEM

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Several clinical studies have suggested that acetylcholine (ACh) plays a role in mediating itch in the periphery; an intradermal injection of ACh induced itch in atopic dermatitis patients. However, it still remains unknown whether ACh and its receptors in the central nervous system are involved in itch. Here we showed that a centrally acting acetylcholinesterase inhibitor, rivastigmine, and a nicotinic ACh receptor (nAChR) agonist, varenicline, significantly reduced itch-associated scratching response induced by an intradermal injection of substance P (SP) in mice without affecting the spontaneous motor activity. These antipruritic effects of rivastigmine and varenicline were suppressed by a selective alpha7 nAChR antagonist, methyllycaconitine, and a non-selective nAChR antagonist, mecamylamine, respectively. In an effort to develop novel therapeutics of itch, we identified selective alpha7 nAChR agonists, TR-P-028 and TR-P-064, which showed significant antipruritic effects in the mouse model of SP-induced scratching without discernable effects on the motor activity. In summary, the present study demonstrates that ACh in the central nervous system functions as an endogenous inhibitor of itch via the activation of alpha7 nAChR and/or other subtypes of nAChRs and that alpha7 nAChR is a potential therapeutic target for itch.

BASIC RESEARCH TRACK– NEURON PROCESSING

PP10

P2X3R-POSITIVE SENSORY NEURONS ARE INVOLVED IN ITCH SENSATION THROUGH A PATHWAY INVOLVING GRP RECEPTORS

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P2X3 receptors (P2X3R), a member of ionotropic purinergic receptors activated by extracellular ATP, are known to be expressed mainly in primary afferent sensory neurons. The role of P2X3R has been extensively studied in pain, but its role in itch is poorly understood. In the present study, we investigated the involvement of P2X3R in itch sensation and its mechanism. We found that intradermal injection of ATP and its analogue αβmeATP (a P2X3R agonist) in the mouse cheek produced a significant increase in scratching behaviors. The scratching evoked by P2X3R agonists was inhibited by A317491, a selective P2X3R antagonist. Furthermore, intracellular Ca2+ imaging of primary cultured trigeminal ganglion neurons showed that αβmeATP evoked Ca2+ responses and that a subpopulation of αβmeATP-responded neurons was responded to an agonist for MrgprA3 that has been implicated in itch sensation. Behaviorally, inactivation of MrgprA3-positive neurons resulted in decreasing the P2X3R-mediated scratching. Moreover, scratching evoked by P2X3R agonists was attenuated in mice lacking receptors for the itch inducer GRP in the spinal dorsal horn. These findings indicate that activation of P2X3R expressed in MrgprA3-positive primary afferents elicits itch sensation through a pathway involving GRP receptors in dorsal horn neurons.

PP11

ASTROCYTIC LIPOCALIN-2 IN THE SPINAL DORSAL HORN IS REQUIRED FOR CHRONIC ITCH

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Chronic itch is a debilitating symptom of skin diseases such as atopic and contact dermatitis. The underlying mechanisms for chronic itch are poorly understood, and identifying the optimal treatment for it is a major clinical challenge. We have recently showed that STAT3-dependent reactive astrocytes in the spinal dorsal horn (SDH) are involved in excessive scratching behaviors in models of atopic and contact dermatitis. However, how astrocytes modulate itch signaling in the SDH is still unknown. In the present study, we identified lipocalin-2 (LCN2) in the SDH of chronic itch models as an astrocytic factor whose expression is up-regulated in a STAT3-dependent manner. Astrocyte-specific knockdown of LCN2 alleviated fully developed chronic itch. Furthermore, intrathecal administration of LCN2 to normal mice increased scratching evoked by intrathecal gastrin-releasing peptide (GRP). These results indicate that LCN2 is an astrocytic STAT3-dependent factor up-regulated in the SDH under chronic itch conditions and play a pivotal role in maintenance of chronic itch by the enhancement of spinal itch signaling involving GRP.

PP12

IN VIVO SPINAL SYNAPTIC RESPONSES AND SCRATCHING BEHAVIORS EVOKED BY CUTANEOUS 5-HT APPLICATION

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Itching is a common symptom in dermatologic diseases and causes restless scratching of the skin, which aggravates the condition. 5-hydroxytryptamine (5-HT) is often used as a pruritic agent in rodents. However, the mechanism for pruritic synaptic transmission in the central nervous system remains elusive. The present study was designed to analyze pruritic synaptic responses evoked by cutaneous 5-HT stimulation in spinal dorsal horn neurons of adult rats by using an in vivo whole-cell patch-clamp recording. Behavioral responses to the 5-HT application were also studied. Topical application of 5-HT to the skin provokes scratching. Under voltage-clamp conditions, topical application of 5-HT to the skin increased the frequency of the large amplitudes of spontaneous EPSCs in about 30% of the neurons recorded. The responses persisted for more than 10 minutes. The large amplitudes of spontaneous EPSCs elicited by cutaneous serotonin stimulation were blocked by either CNQX or TTX applied to the surface of the spinal cord. Under current-clamp conditions, topically application of 5-HT increased the frequency of large amplitude of EPSPs, some of which elicited a burst of action potentials. These observations suggest that a subpopulation of superficial spinal dorsal horn neurons convey pruritic excitatory information to provoke scratching behaviors.

BASIC RESEARCH TRACK – NEUROPATHIC ITCH

PP13

EVALUATION OF THE PRURITOGENIC ROLE OF IL-13 IN MICE

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The role of cytokines as mediators of neuro-immune communication and therapeutic targets for itch is emerging. Interleukin 13 (IL-13) is a Th2-dominanted cytokine and considered to be a critical mediator of human allergic disorders including atopic dermatitis (AD). The cellular mechanisms of IL-13-mediated itch are poorly defined. We tested the pruritogenic effect of IL-13 in the mouse cheek model in vivo, and determined signaling pathways of IL-13 in murine dorsal root ganglia (DRG) neurons. Significant dose-dependent increase of scratching behavior was observed in IL-13 injected mice compared to controls. We evaluated the gene expression of IL-13 and its receptor in the trigeminal ganglion (TG) in a mouse model of chronic AD. Both IL-4RA and IL-13RA1, components for the IL-13 receptor, were expressed in TG in normal mice. Moreover, the expression of both genes was up-regulated in conditional keratinocyte-PAR2 overexpressed mice, suggesting a role of IL-4RA and IL-13RA1 in chronic AD. Functional studies indicated several cell signal transduction pathways involved in IL-13-induced itch. These results suggest the Th2 cytokine IL-13 to be a critical mediator in murine itch transduction and may be a promising therapeutic target for pruritus disorders and that dupilumab acts directly on sensory neurons to block itch.

BASIC RESEARCH TRACK – INFLAMMATION

PP14

THE EFFECTS OF CATHELICIDIN LL-37 ON SEMAPHORIN 3A EXPRESSION IN NORMAL HUMAN EPIDERMAL KERATINOCYTES

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Epidermal nerve density is greater in the lesional skin of patients with atopic dermatitis (AD) than in healthy individuals. The hyperinnervation is partly involved in peripheral itch sensitization.

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

PP15

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

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

CLINICAL RESEARCH TRACK – METHODOLOGY FOR ITCH

PP16

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

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

CLINICAL RESEARCH TRACK – PRURIGO AND OTHER PRURITIC SKIN

PP17

CORRELATION OF PLASMA GRANZYME B LEVELS WITH PRURITUS OF ATOPIC DERMATITIS

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

CLINICAL RESEARCH TRACK – QUALITY OF LIFE

PP18

PATIENT NEED FOR PRURITUS REDUCTION IN DERMATOLOGICAL DISEASES

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Background: Chronic pruritus is a frequent symptom in dermatological patients. The current study takes an in-depth look at the relevance of pruritus-associated therapeutic needs. *Methods:* Data of 500 patients, treated in a German university hospital for ten different dermatological diseases were analysed with descriptive methods and variance analysis. The importance of 23 therapeutic needs was measured on a five-point scale from 0–4 using the Patient Needs Questionnaire of the Patient Benefit Index (PBI). Herein three pruritus-associated needs regarding itching, burning and pain were assessed. *Results:* The mean need level was 2.65. The need "to be free of itching" presented a mean need level of 2.46 (rank 15), "to be free of pain" of 2.56 (rank 12) and "no longer have burning sensations on the skin" of 2.33 (rank 18). Patients with eczema, urticaria or psoriasis had a higher need for pruritus reduction, patients with herpes zoster for pain reduction ($p<0.05$). Patients suffering from hyperhidrosis, hair diseases, or acne had a lower need for the reduction of burning sensations or pain ($p<0.05$). *Conclusions:* The needs for the reduction of pruritus-associated symptoms are ranked within the lower third of twenty-three treatment goals, but the importance is significantly different between dermatological diseases.

PP19

ITCH IN CHRONIC URTICARIA

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Urticaria is one of the most common skin diseases. Despite itching is the most important symptom of urticaria, data on the influence of itch on the patient psychosocial wellbeing in urticaria are limited. Recently, we have performed a large multicenter study to provide more insights on itch in chronic urticaria. A total of 1091 adults (709 women and 382 men) with chronic urticaria have been included into the study. All patients were asked to complete the Dermatology Life Quality Index (DLQI), Work questionnaire (Q-Work), Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), Athens Insomnia Scale as well as to assess pruritus with visual analogue scale (VAS) and 4-item itch questionnaire (4-IQ). No significant differences were observed between patients with inducible and chronic spontaneous urticaria regarding pruritus intensity assessed with VAS (6.8±2.3 vs. 6.7±2.4 points, $p=0.26$). Pruritus intensity significantly correlated with patients QoL (r=0.3 to 0.42), problems with sleeping (r=0.33 to 0.44), and, to lesser degree, with decreased work activity (r=–0.23 to –0.11). Our large epidemiological study clearly indicated, that patients with chronic urticaria often demonstrate impaired QoL, and the QoL alteration is independent on the urticaria type, but is rather related to pruritus severity.

PP20

CHARACTERIZATION OF THE QUALITY OF LIFE IMPACT OF CHRONIC ITCH IN PEDIATRIC PATIENTS

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Background: Pruritus is a difficult symptom to treat. Insight into patients' experiences of itch can help determine treatment and clinical improvement. *Methods:* Children, 8–17 years old, completed surveys about the impact of chronic itch during the past week. They were asked about 35 quality of life issues divided between social, emotional and functional categories. Initial analysis includes 8 patients but will eventually include 135 patients. *Results:* Certain experiences were more universally reported across the group. Not unexpectedly, all patients reported scratching (100%) and use of lotions (100%). Interestingly, 100% of patients reported worsening itch with changing seasons. The social impact was substantial with patients reporting trouble focusing on schoolwork (75%), feeling stared at by others (75%), inability to play outside (75%) and worry about what others thought (75%). The emotional consequences were narrower, with patients most frequently feeling frustrated (88%) and "driven crazy" (75%). When addressing skin symptoms, the most frequent were pain (75%) and scarring (88%). *Conclusion:* There was consistency in several factors affecting quality of life, particularly social aspects. It is evident that chronic itch has a substantial impact on social functioning. Evaluating more patients will better clarify the influence on quality of life.

CLINICAL RESEARCH TRACK – NEUROPATHIC ITCH

PP21

CLINICAL CHARACTERISTICS OF PRURITUS IN NEUROFIBROMATOSIS 1

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Neurofibromatosis 1 (NF1) is a cause of neuropathic pruritus. Approximately 20% of NF1 patients suffer from pruritus. However, little is known about its characteristics. A questionnaire about the characteristics of pruritus was given to patients with NF1 who complained of pruritus. Forty-one patients were included in the study. Pruritus was located in the area of neurofibromas in 52.5% of the patients and elsewhere on the skin for 47.5% of the patients and was heterogeneous, localized, more diffuse or generalized. Itch sensations were frequent, occurring daily or almost daily for most patients and more frequently in the evening. The intensity was moderate but impaired the patients' quality of life. Other sensory symptoms (such as burning) were not frequent. Typically, daily activities had no effect on pruritus. Sweating, skin dryness, specific fabrics and stress often increased pruritus. Concerning scratching, 87.5% of the patients scratched their skin "very often" or "often", which was pleasurable for most of them. Our study provides more information on the characteristics of pruritus in NF1. It is useful

to better understand patients' experiences. This symptom could be taken into account in the quality of life scale. Pruritus is a poorly known but crucial symptom of NF1.

CLINICAL RESEARCH TRACK – THERAPEUTICS

PP22

SAFETY AND ANTI-PRURITIC EFFICACY OF A MENTHOL-CONTAINING MOISTURIZING CREAM

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Background: Itch is frequently associated with dermatoses characterized by a defective skin barrier. We formulated an itch-relieving moisturizing cream containing 3% menthol and ceramides. *Aims:* To evaluate the safety and anti-pruritic efficacy of application of this cream in volunteers with and without skin diseases. *Methods:* Volunteers were to apply the cream for 1 month on a minimum body surface area of 6%. Safety was assessed by the absence of contact dermatitis or other side effects, using a self-administered questionnaire administered at 5 minutes, 1 week and 1 month after application. To assess efficacy, volunteers with pruritic dermatoses were to grade their average itch intensity at baseline, 1 week and 1 month after application. *Results:* Sixty volunteers were recruited, of whom 41 had no skin disease. There were no adverse events reported in the latter. Of the 19 volunteers with dermatoses, 18 reportedly had eczema. One stopped application due to stinging sensations induced by menthol. Itch scores of volunteers with eczema improved from baseline at 1 week (p=0.01) and 1 month (p<0.01) after application. *Conclusion:* Application of a 3% menthol-containing moisturizing cream was safe in healthy individuals and individuals with eczema. In the latter, application of the cream significantly reduced itch scores.

PP23

PLEIOTROPIC ACTION OF CYCLOSPORINE ON PRURITUS OF ATOPIC DERMATITIS

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Cyclosporine A (CsA) is currently used in treatment of patients with severe atopic dermatitis (AD) and suppresses the pruritus, although its antipruritic mechanism is poorly understood. This study was performed to reveal the antipruritic mechanism of CsA in AD using a mouse model of AD induced by repeated application of house dust mite Dermatophagoides farinae body (Dfb) ointment (Dfb-NC/Nga). Intraperitoneal injection of 5 mg/kg CsA significantly reduced epidermal nerve density, number of scratching bouts, dermatitis scores, and transepidermal water loss, as well as decreasing the numbers of CD4+ T cells, mast cells, and eosinophils in the dermis and decreasing epidermal thickness. Moreover, intraperitoneal injection of CsA dose-dependently inhibited increased itch-related receptor gene expression, such as interleukin-31 receptor A (IL-31RA) and neurokinin-1 receptor (NK1R), in the dorsal root ganglion (DRG) of Dfb-NC/Nga mice. Thus, the therapeutic efficacy of CsA in pruritus of AD may involve reduced epidermal nerve density and expression levels of IL-31RA and NK1R in the DRG as well as improvement of acanthosis and reduction of cutaneous inflammatory cell numbers.

PP24

DECREASE OF ITCH INTENSITY BY CR845, A NOVEL KAPPA OPIOID RECEPTOR AGONIST

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Kappa opioid agonists are known to modulate pruritus and the mixed non-selective mu partial agonist/kappa opioid agonist nalfurafine (Remitch™) is marketed in Japan for the treatment of uremic pruritus (UP) in hemodialysis patients. CR845 is a new kappa opioid receptor agonist being developed for the treatment of UP. In addition to its unique receptor profile (no activity at mu- or delta-opioid receptors), the peptidic structure of CR845 restricts its entry into the central nervous system and differentiates it from other therapies such as nalfurafine. A dose-dependent, sustained anti-itch activity was demonstrated for CR845 using in vivo mouse models of itch (induced by the selective KOR antagonist, 5'-GNTI, and the mast cell secretagogue, compound 48/80). IV CR845 was also evaluated in a double-blind, randomized, placebo-controlled trial in the US with 65 patients with moderate to severe UP. At the end of a two-week treatment period (administration 3 times/week after each dialysis), a significant reduction in itch intensity (as measured by a visual analog scale) was reported in patients receiving CR845 (1 μg/kg, n=33) compared to those receiving placebo (p=0.016, n=32). These results provide evidence that selective activation of peripheral kappa opioid receptors reduces itch.

CLINICAL RESEARCH TRACK – CLINICAL CASES

PP25

CONSIDERABLE VARIABILITY IN THE EFFICACY OF 8% CAPSAICIN TOPICAL PATCHES IN THE TREATMENT OF CHRONIC PRURITUS IN 3 NOTALGIA PARESTHETICA PATIENTS

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Notalgia paresthetica is a relatively common focal neuropathic itch condition (IFSI classification III) manifesting in intense chronic or recurrent episodic itch in a hyperpigmented, macular, uni- or bilateral skin area frequently located below and/or medially to the scapulae. Achieving satisfactory relieve in notalgia paresthetica patients is highly challenging. In this case series three female notalgia paresthetica patients were treated with 8% capsaicin capsaicin patches following a spatial quantification of their alloknetic area with a 10 g von Frey filament. The use of a von Frey filament in order to delimit the precise area of itch, itch sensitization and thus patch application, proved clinically feasible. Although 8%

topical capsaicin relieved itch in all three patients, the duration of the effectiveness varied greatly from only 2–3 days to >2 months. The treatment was well tolerated by the three notalgia paresthetica patients and there appear to be no significant hindrances to applying this treatment with notalgia paresthetica as an indication, although it may only exhibit satisfactory effectiveness in certain patients. Placebo-controlled double-blinded trials are needed to confirm the effectiveness of the treatment and assess potential predictive parameters of the treatment outcome.

PP26

IMPACT OF PSEUDO-CERAMIDE CONTAINING MOISTURIZER ON THE ITCH INTENSITY IN SUBJECTS WITH ATOPIC DERMATITIS

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Dry skin in atopic dermatitis (AD) has been thought to contribute to cause itch. It has been reported that ceramide-content decreased in stratum corneum of AD, and contributes to the skin drynesss. To investigate the impact of topical application of ceramide on itch, we conducted a randomized placebo-controlled bilateral comparative study. Moisturizers with or without pseudo-ceramide were allocated in randomized manner to fore arms (especially cubital fossa) of subjects with mild and moderate AD (n=9) for 4 weeks. At the point of 0 week, 2 weeks and 4 weeks after initiation of this protocol, skin manifestations (e.g, itch VAS score, drynesss, erythema, excoriation, water holding capacity ,TEWL, threshold temperature and axon reflex-mediated sweating volume measured by quantitative sudomotor axon reflex test (QSART)) were evaluated. In the result, both pseudo-ceramide containing or placebo creams improved drynesss. On the one hand, pseudo-ceramide containing cream apparently reduced itch VAS score compared to the placebo cream. This indicated that the topical pseudo-ceramide application will contribute to itch effectively.

CLINICAL RESEARCH TRACK – CLINICAL TRIALS

PP27

HAS SERTACONAZOL 2% AN ANTIPRURITIC EFFECT IN ATOPIC DERMATITIS?

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Sertaconazole has been reported to have direct immunomodulatory effects, which could possibly explain part of its antipruritic effect in fungal infections. However, little is known about its antipruritic effect in other pruritic skin diseases like e.g. atopic dermatitis. Therefore, we conducted a randomized, double-blind, placebo controlled, clinical trial to assess the antipruritic effect of topical sertaconazole 2% cream in atopic dermatitis patients, who applied one of the two treatments twice daily during four weeks on pruritic AD skin. Primary efficacy success was defined as ≥ 2 grades pruritus intensity reduction (VRS) between baseline and week 4. Further efficacy variables were, pruritus intensity and insomnia (both VAS), state of atopic dermatitis (SCORAD) and of quality of life (DLQI). 16% of patients in the active group and 21% in the placebo group achieved the primary objective. Pruritus intensity as evaluated by VAS decreased slightly but not significantly more in the active group. Overall, no significant difference between sertaconazole 2% and placebo could be observed for any of the evaluated itch and itch related parameters.

PP28

IDIOPATHIC PRURITUS AMONG ELDERLY FRENCH OUTPATIENTS: CHARACTERISTICS AND IMPACT OF AN EMOLLIENT

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The prevalence of pruritus is high among the elderly, but surprisingly has been rarely studied in France. This pilot study was performed to describe pruritus among elderly French people and to assess the impact of an emollient. 15 patients aged 78.80±9.19 years suffering from chronic idiopathic pruritus were enrolled. 46% experienced pruritus at least once per day. The arms were the most common sites where patients experienced pruritus (93.3%). In most cases (60%), a predisposing factor was found. After 2 weeks of emollient application, pruritus intensity was decreased as measured by VAS (p=0.0015) and a validated questionnaire (p<0.0001) and xerosis was improved (4-point grading scale (p=0.0002)). Cathepsin S, whose role in some pruritic inflammatory dermatoses is described, was assessed by taking cotton swab samples of skin on itching sites. Before treatment, Cathepsin S levels were similar to those of a population without pruritus or xerosis and remained unchanged after 2 weeks of treatment (p=0.838) suggesting that Cathepsin S is not involved in pruritus in the elderly. This pilot study validated the efficacy of an emollient in reducing pruritus intensity among elderly patients and suggested that Cathepsin S is not a relevant marker of pruritus in this population.

PP29

THE POSITIVE IMPACT OF MEDITATION ON QUALITY OF LIFE FOR PATIENTS WITH CHRONIC PRURITUS: A PILOT TRIAL

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Background: Chronic itch is a debilitating problem with exceedingly few medical therapy options. Meditation has been shown to reduce neuroendocrine and inflammatory markers. This study investigates the impact of meditation on chronic pruritus and quality of life (QoL). *Methods:* Seven adults with chronic pruritus participated in an 8-week meditation course. Four patients (57%) completed the course, defined as class attendance >75%. QoL was evaluated with a validated, self-reported questionnaire (ItchyQoL) before and after the course. The test reports a summative score

ranging from 1–5. Patients kept a journal of time spent in meditation outside of class. *Results:* Overall, ItchyQoL scores improved an average of 0.50 points (p=0.014). Those who practiced outside of class >1 hour/week improved by 0.48 (p=0.047). Those patients who completed the course improved 0.34 points (p=0.042). When considering subscales of questions, five out of nine emotional questions had significant changes after intervention. Functional and symptomatic questions did not improve significantly. *Conclusion:* Meditation decreased the impact of pruritus on the quality of life, particularly the emotional component. Meditation outside of class had a greater impact than completion of a formal course. Larger studies are needed to investigate the impact of meditation on itch QoL.

CLINICAL RESEARCH TRACK – EPIDEMIOLOGY

PP30

STRESS AND ITCH IN COLLEGE STUDENTS: RESULTS OF A WEB-BASED QUESTIONNAIRE STUDY

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Background: Skin symptoms and diseases have been associated with stress. This study is the first analyzing this relationship in a large sample of college students. *Methods:* A representative sample of 5,000 undergraduate students was invited to take part in a web-based survey (n=482 total responses, n=425 students were included in the analyses due to missing data). The Perceived Stress Questionnaire and Questionnaire on Self-reported Skin Complaints were used to assess stress and skin symptoms over a month`s period. Students were split in to low (LS; ≤ 25th percentile), medium (MS; > 25th and ≤ 75th percentile) and high stress (HS; > 75th percentile) groups. *Results:* Itch was one of the most common skin complaints, with 58% reporting itch. HS subjects suffered from significantly more pruritus compared to the LS group (adjusted OR 2.79 (1.58–4.94); p<0.001). Compared to LS, HS students were affected more often with scaly skin, itchy rash on hands, troublesome sweating, hair loss, oily/flaky patches on the scalp, nail-biting, and hair-pulling (all p<0.05). *Conclusion:* High stress was associated with a greater prevalence of pruritus and other dermatological issues. Future studies should investigate the neuroendocrine mechanisms responsible for these effects.

PP31

ANTIHISTAMINE USE IN PATIENTS WITH CHRONIC HAND ECZEMA? AN ANALYSIS BASED ON DATA FROM THE GERMAN CARPE REGISTRY

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Antihistamines (AH) are often prescribed in skin diseases but there is no evidence base for the use in chronic hand eczema (CHE). Nevertheless, the CARPE registry shows that CHE patients report having used AH. This analysis aims to identify factors associated with AH use in patients with CHE. AH use in the past 12 months was considered as outcome variable. Clinical, demographic and treatment-related variables were considered as predictive factors. 25% of the sample (n=1,255 patients, 54.1% female; mean age: 47.1 years) reported to have used AH in the past 12 months. Significant positive associations with AH use were identified for severe itch (OR=4.27, 95% CI 2.40–7.59), a history of systemic treatment (e.g. alitretinoin) (OR=2.85, 95% CI: 2.06–3.96), flexural eczema (OR=1.89, 95% CI 1.32–2.71), allergic rhinitis/conjunctivitis (OR=2.41, 95% CI 1.71–3.39), and female sex (OR=1.58, 95% CI 1.16–2.14) in multivariate analyses (n=1,184). Significant inverse associations were found for an eczema localization besides the hands (OR=0.66, 95% CI 0.46–0.94) and for patients being recruited in hospital (versus private practice; OR=0.72, 95% CI 0.33–0.67). This study suggests that AH use is frequent in patients with CHE and mainly related to female sex, disease severity, itch, co-morbid atopic disease and treatment in private practice.

PP32

UNMET MEDICAL NEED AND DURATION OF CHRONIC SEVERE ITCH REPORTED BY COMMUNITY DERMATOLOGISTS IN THE UNITED STATES

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Background: Chronic pruritus (CP) is a common complaint received by dermatologists. There are few studies on the epidemiology of CP. Objectives We sought to understand the level of unmet medical need for CP and the length of time patients with severe and very severe CP (SCP) had experienced the symptom. *Methods:* 3,577 US dermatologists from an AMA database were invited to participate in an email screener that queried patient load for various dermatological conditions, without revealing pruritus was the focus of the screener. 275 of 291 respondents reported 10 or more CP patients per year. These respondents then participated in an on-line questionnaire containing 55 questions. 212 of 275 respondents completed the survey. *Results:* Surveyed dermatologists reported CP having the highest unmet medical need (8.6 on scale of 1–p<10) compared to other dermatological conditions. Of patients with SCP, physicians reported the following percentages for their symptom duration: 6 weeks–6 months (20%), 6 months–1 year (26%), >1 year–5 years (35%) and >5 years (19%). *Conclusions:* Dermatologists rate the unmet medical need for CP highest amongst dermatologic conditions and report the duration of SCP lasting more than one year in 54% of cases.

PP33

PRURITUS MEDICAL RESOURCE UTILIZATION IN US VETERANS

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Despite the pervasiveness of chronic pruritus, the economic impact of this potentially debilitating symptom is unknown. We sought to quantify medical resource use due to chronic pruritus through data from our US Veterans Pruritus Study. Medical resources included physicians' visits, medications, and alternative therapies. We also investigated lost time due to symptoms. A total of 405 veterans reported chronic pruritus within the last year; 4% reported no itching, while others reported mild (22%), moderate (56%) or severe (18%) itching in the preceding week. For their pruritus, 23% of patients saw their primary care provider (range of 1–15 visits) and 17% saw a specialist (range of 1–36 visits) within the preceding 3 months. Additionally, 13 patients (3%) went to an emergency room (range of 1–5 visits). Notably, 10% of patients spent over 30 minutes a day treating their symptoms, and 14% required extra help in completing household tasks. For medications, 62% of patients used an over-the-counter topical, and 45% used a prescription topical. 13% used an over-the-counter oral and 13% used a prescription oral medication. Overall, the data show that pruritus symptoms result in a substantial amount of medical resource use and potential indirect costs. Future efforts will quantify these costs.

PP34

DEFINING BANDS OF THE ITCHYQUANT: A PILOT STUDY

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Methods: Seventy-two adults with pruritus were recruited from Emory University, Oregon Health and Science University, Temple, and Rush. Patients were asked to rate their itch on the ItchyQuant and categorize their itch as "no, mild, moderate or severe." One-way ANOVA with *post-hoc* Tukey HSD testing was performed to determine if average ItchyQuant scores in each category significantly differed. Analysis of a scatterplot allowed for estimation of bands. *Results:* Analysis of a scatterplot suggests setting the bands as follows: 1–4 (mild), 5–7 (moderate), 8–10 (severe). One-way ANOVA showed a significant difference in the bands (3.71 (SD 1.40) vs. 6.16 (SD 1.45) vs. 9.10 (SD 1.37), $p<0.0001$). *Post-hoc* analyses demonstrated patients with moderate itch significantly differed from those with mild ($p=0.0002$) or severe itch ($p<0.0001$). *Conclusion:* Our pilot data suggest the ItchyQuant can be banded in a manner to represent clinically meaningful categorization of itch severity. More rigorous statistical analysis is required to determine the appropriate cut-offs for these bands.

PP35

DOES UREMIC PRURITUS INFLUENCE ALEXITHYMIA?

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The aim of this study was to assess the relationship between pruritus and alexithymia in hemodialysis patients. The study was conducted in 90 hemodialysis patients (48 with uraemic pruritus, 42 without pruritus). Alexithymia was evaluated using the Bermond-Vorst Alexithymia Questionnaire (BVALQ). Pruritus intensity was assessed using the visual analogue scale (VAS). No significant differences were found between patients with and without pruritus regarding the total score of BVALQ 103.5–13.9 vs. 108.5–16.3 points ($p=0.12$), respectively. However, there was a statistically significant difference considering the subscale of daydreaming and fantasy. Patients with uraemic pruritus had significantly lower average score in this subscale 25.9–11.1 vs. 21.7–8.9 points ($p<0.05$), respectively. Moreover, the scoring in this domain negatively correlated with the intensity of pruritus ($r=-0.33$, $p=0.03$). The ability to fantasize and daydream is higher in patients with uremic pruritus compared to patients without pruritus and correlates with the intensity of pruritus.

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