

Report from the 4th International Workshop for the Study of Itch

Gil Yosipovitch¹ and E. Carstens²

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The 4th International Workshop for the Study of Itch* was held 9–11 September 2007 in San Francisco, California. For the first time, the meeting was sponsored in part by a grant from the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the Office of Rare Diseases of the National Institutes of Health. Also for the first time, the meeting was held under the auspices of the International Forum for the Study of Itch (IFSI). Organized by Earl and Mirela Carstens, the meeting was attended by more than 130 scientists and physicians from throughout the world. The workshop covered a vast range of topics, including the neurophysiology of itch in humans and animals, molecular mechanisms of itch, neurogenic inflammation, and pharmacology of antipruritics. Clinical aspects were well covered, and there was a lively discussion of itch definitions. Other topics included clinical research on the epidemiology and pathophysiology of itch in systemic disease, neuropathic itch, new treatments, and psychosocial aspects of chronic itch. Highlights of the meeting are presented below.

Itch neurophysiology

Since the discovery 10 years ago of unmyelinated (C-fiber) afferents in humans that are selectively responsive to histamine but mechanically insensitive, it has been debated whether these fibers are the only ones that transmit itch. Clinically, it is well known that potent oral antihistamines do not relieve most types of itch. Moreover, mechani-

cal stimuli can evoke itch, prompting a renewed and timely effort to discover new itch fibers. Collaborating neuroscientists from Yale, John Hopkins, and the University of Minnesota were able to demonstrate the existence of novel populations of peripheral afferent fibers, as well as spinothalamic tract neurons in primates, that respond to cowhage, the “velvet” bean plant whose pods contain spicules that were demonstrated to induce cutaneous itch more than 50 years ago by Walter Shelly. Mathias Ringkamp (John Hopkins University, Baltimore, MD) presented data from human psychophysical studies demonstrating that cowhage spicules induced itch without flare. Topical antihistamines did not inhibit this itch, but capsaicin, a C-fiber depletor, did. Glenn Giesler and colleagues at the University of Minnesota (Minneapolis) presented new data on a subpopulation of identified spinothalamic tract (STT) neurons in primates that were activated by cowhage over a time course matching that of itch in humans. These neurons also responded to noxious mechanical and thermal stimuli but did not respond to histamine. A different subpopulation of STT neurons was unresponsive to cowhage, but responded to histamine again over a time course matching that of itch sensation. Their data suggest the existence of separate populations of STT neurons that signal itch of different origins to several thalamic nuclei involved in encoding itch.

Gil Yosipovitch (Wake Forest University, Winston-Salem, NC) presented data from a study using a new

brain imaging technique—arterial spin labeling—that appears better suited to evaluate itch than functional magnetic resonance imaging or positron emission tomography. Atopic eczema patients suffering from chronic itch exhibited significant differences from healthy control subjects in the distribution of brain areas that were active both under baseline conditions and during histamine-evoked itch.

Molecular mechanisms of itch and genetic models

Zhou Feng Chen (Washington University, St. Louis, MO) presented findings using a differential screening technique to identify gastrin-releasing peptide receptor (GRPR) as a candidate neurotransmitter in the superficial spinal dorsal horn that is involved in itch transmission. GRPR is a G protein-coupled receptor derived from the *bombesin* family. Mutant mice lacking GRPR exhibited significantly less scratching behavior in response to three pruritic agents—histamine, protease activated receptor-2 (PAR-2) agonist, and chloroquine—in a manner that was reversed by GRPR antagonists. The mutant mice displayed normal nociceptive responses to noxious thermal and mechanical stimuli or tissue inflammation.

Jeffrey Mogil (McGill University, Montreal, Canada) discussed the role of genetic factors in the variability of histamine- and chloroquine-evoked scratching among 11 different inbred mouse strains, which differed up to 2.5-fold. Furthermore, he demonstrated that female mice exhibited significantly

¹Departments of Dermatology, Neurobiology, and Anatomy, Wake Forest University Health Sciences, Winston-Salem, North Carolina, USA; and ²Section of Neurobiology, Physiology, and Behavior, University of California, Davis, Davis, California, USA

Correspondence: Dr Gil Yosipovitch, Department of Dermatology, Wake Forest University Health Sciences, Medical Center Boulevard, Winston-Salem, North Carolina 27157, USA. E-mail: gyosipov@wfubmc.edu

more pruritogen-evoked scratching (by 23%) compared with male mice. He also provided evidence for a negative correlation between itch and pain, such that mouse strains exhibiting greater sensitivity to noxious stimuli exhibited less scratching, and vice versa. These findings may lead to the future identification of itch-related genes.

Makoto Tominaga (Okazaki Institute, Tokyo, Japan) presented an overview of the possible role of thermosensitive transient receptor potential (TRP) channels in itch. He also presented data demonstrating that skin keratinocytes express a variety of thermoTRP channels and may be involved in detecting temperature and pruritic stimuli along with sensory nerve fibers.

Neuromodulators and itch

Martin Steinhoff (University of Münster, Germany) presented an overview of the mediators of neurogenic inflammation and the cross-talk among mast cells, dendritic cells, and T cells involved in the itch response. Mediators such as endothelin-converting enzyme 1 and neutral endopeptidase control substance-P degradation and neurokinin-A-mediated signaling of inflammation and itch. An important role for proteases and their respective PAR receptors was initially reported by Steinhoff 7 years ago and continues to be extensively investigated by his group. Interactions with interleukin-31, a cytokine recently found to be a pruritogen in atopic eczema, were mentioned as potential targets for future antipruritic medications.

Yashushi Kuraishi (Toyoma University, Japan) presented data that refuted the common notion that mosquito-bite itch is solely histamine-

mediated. He reported that the voltage-dependent calcium channel $\alpha_2\delta$ -1 subunit is involved in itch signaling by afferent nerve fibers of mice with allergic itch induced by an extract of mosquito salivary gland. Gabapentin reduced scratching evoked by mosquito salivary gland extract, but not histamine, in a dose-dependent manner. This calcium-channel subunit was extensively coexpressed with the capsaicin and heat receptor TRPV1 in sensory neurons. A poster from the same group demonstrated that itch associated with hypersensitization to mosquito bites is mediated by a lipoxin A_4 (LXA), a 5-lipoxygenase metabolite. Furthermore, mice with hypersensitivity to mosquito bites had elevated CD4 T cells with receptors for LXA. These CD4 cells induced LXA $_4$ itch in mice.

Treatments for itch

Several new antipruritic treatment modalities were presented at the meeting. One of the new concepts is that an imbalance in central μ - and κ -opioids may play a role in chronic itch. Support for this concept was presented by Hiroshi Umeuchi (Toray Industries, Urayasu, Japan) in a study of 59 patients with primary biliary cirrhosis (PBC), a cholestatic liver disease that is associated with severe itch. Patients experiencing itch exhibited higher plasma concentration of μ -opioids compared with patients not experiencing itch. In a mouse model of PBC, nalfurafine hydrochloride, a κ -agonist, significantly inhibited scratching behavior. Kenji Takamori (Juntendo University, Urayasu, Japan) reported the results of a large double-blind study using nalfurafine in 337 hemodialysis patients

with pruritus resistant to other treatments. The results demonstrated significant reduction in itch intensity with a rather safe profile.

Sonja Ständer (University of Münster, Germany) presented results of a large, open-label study of 72 patients with chronic itch of different origins. The selective serotonin reuptake inhibitors paroxetine and fluvoxamine significantly reduced itch in more than 50% of patients.

A major highlight of the workshop was the Handwerker Prize, awarded to a junior scientist whose poster was voted best by an impartial committee. The prize is named in honor of Hermann Handwerker (University of Erlangen, Germany), a pioneer in the field of itch research who has trained many neuroscientists in the field. The award was given to Steve Davidson (University of Minnesota, Minneapolis), who showed that scratching reduced the histamine- and cowhage-evoked responses of primate STT neurons in a manner consistent with the ability of scratching to relieve itch.

The 5th International Workshop for the Study of Itch is scheduled to take place in Kyoto, Japan, 25–28 October 2009, and will be organized by Kenji Takamori of Juntendo University, Urayasu, Japan. For more information about future meetings, visit the IFSI online at <http://www.itchforum.org>.

CONFLICT OF INTEREST

Dr. Yosipovitch served as a consultant and member of the advisory board of Acologix, which is developing a κ -agonist for the treatment of itch.

**The 4th International Workshop for the Study of Itch was held at the Hilton San Francisco Financial District in San Francisco, California, USA, 9–11 September 2007.*