# Stimulus-response evaluation of the antipruritic effect of homotopic, monophasic cold and TRP-agonist counter-stimulation on histamine-induced itch in healthy volunteers

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

*Published in:*
Acta Dermato-Venereologica

*DOI (link to publication from Publisher):*
10.2340/00015555-2211

*Publication date:*
2015

*Document Version*
Publisher's PDF, also known as Version of record

# 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

*Yuhki Ueda[1], Kei Hashimoto[1], Takamichi Kitano[1], Kido Hiroko[1], Tatsumi Matsumoto[1], Ritsuko Ishii[1], Keiji Imoto[2], Hidemasa Furue[2]*

*[1]Maruho Co., Ltd., Kyoto R&D Center, Kyoto, [2]Department of Information Physiology, National Institute for Physiological Sciences, Okazaki, Japan*

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

*Hideki Funahashi[1], Rumi Naono-Nakayama[2], Yu Miyahara[1], Yasushi Ishida[1], Toshikazu Nishimori[1]*

*[1]Dep. psychiatry Psychiatry, Fac. Medicine, Univ. Miyazaki, [2]Div. Integrative Physiology, Fac. Medicine, Univ. Miyazaki, Miyazaki, Japan*

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]*

*[1]Center for Sensory-Motor Interactions, Department of Health Science and Technology, Aalborg University, Aalborg, [2]The Allergy Clinic, Copenhagen University Hospital, Gentofte, Copenhagen, Denmark*

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.