EJP
European Journal of Pain

MINI REVIEW

Evolving understanding on the aetiology of thermally provoked itch

H. Murota, I. Katayama

Department of Dermatology, Course of Integrated Medicine, Graduate School of Medicine, Osaka University, Suita, Japan

Correspondence
Hiroyuki Murota
E-mail: h-murota@derma.med.osaka-u.ac.jp

Funding sources
H.M and I.K. received research grant support from the Ministry of Health, Labour, and Welfare, Japan. H.M. received research grant support from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Conflicts of interest
None declared.

Accepted for publication
8 August 2015

doi:10.1002/ejp.777

Abstract

Background and objectives: Itch is one of the major symptoms in dermatology clinics, and severely impairs the quality of life. Itch is frequently produced by environmental stimuli, especially heat or warmth. Changes of temperature on the skin surface and noxious heat stimuli augment and develop itch, respectively. Thermally provoked itch is sometimes intractable with existing treatments.
Data bases and data treatment: Recent researches, linking heat sensation and itch, were searched in MEDLINE literature database through PubMed.
Results: Recent studies of the transient receptor potential cation channel subfamily vanilloid type 1 (TRPV1), the calcitonin gene-related peptide (CGRP) and the vesicular glutamate transporter 2 (VGLUT2), which link noxious heat and itch, contribute to a much better understanding of the thermally evoked itch process. From a clinical perspective, a warm sensation is a major provocative factor for subjects with atopic dermatitis. The accumulation of artemin (also known as enovin or neublastin) in the dermis of lesional skin can possibly provide a pathological mechanism for warmth-provoked itch.
Conclusions: This mini-review describes recent results of both basic and clinical research related to thermally provoked itch.

Itch is defined as an unpleasant cutaneous sensation which provokes the desire to scratch (Rothman, 1941). Itch has been studied as contrasting with the sensation of pain. From the 19th to 20th century, itch had been thought of as a minor form of pain (Handwerker, 2014). This theory regarded itch as a pain, by definition, but did not argue that itch is independent from pain. There are some facts that disagree with this theory: First, strong itch does not induce pain, second, morphine and certain opioids reduce pain but cause itch, and third, behavioural responses to pain are avoidance responses, while responses to itch are scratching. These results indicate that itch is essentially different from pain (Handwerker, 2014). Itch has an important role for living organisms. It is thought that itch contributes to a sense of danger to the skin surface (Stante et al., 2005). For example, living organisms may feel an itch on the skin surface and will subsequently scratch, producing a behaviour that removes the dangerous object. Thus, the itch sensation is a host defence mechanism (Stante et al., 2005).

Environmental factors (e.g. temperature, humidity, and atmosphere), living habits (e.g. bathing, sweating activities, and clothing worn), and the state of mind (e.g. psychological stress, or fatigue due to sleep loss) can be inducers of the itch response. Among these factors, heat or warmth stimuli may be the major factors that provoke the itch response (Wahlgren, 1991). Recent studies have identified a relationship between heat/warmth sensations and itching. The transient receptor potential vanilloid type 1 (TRPV1) protein has been linked to itch and heat sensations. The TRP family is a non-selective ion channel family of proteins localized on the cell membrane. TRP proteins respond to outer cell

What does this review add?

- This review focused on the thermally provoked itch response, and reviewed current research on the clinically relevant mechanisms.

temperature, thus allowing cations to flow into the cell. TRPV1 is activated by heat (above approximately 42 °C), capsaicin and protons, and is involved in the induction of histaminergic-related itch responses (Tominaga and Caterina, 2004). Histamine activates the arachidonic acid cascade, to subsequently form 12-hydroperoxyeicosatetraenoic acid (12-HPETE), inducing the histaminergic itch response by activating TRPV1 (Kim et al., 2007; Shim et al., 2007). Furthermore, the scratch behaviour following histamine administration is diminished in TRPV1 knockout mice (Kim et al., 2007). Several inflammatory mediators, including bradykinin, adenosine, serotonin, prostaglandins and ATP, are known to sensitize TRPV1, and can reduce the temperature threshold for TRPV1 activation (Tominaga and Caterina, 2004). Skin inflammation will result in thermal hyperalgesia by sensitized TRPV1, and therefore comparatively low temperatures (non-painful in normal skin) could induce itch. TRPV1 lineage neurons play a prominent role in thermosensation, thermoregulation and nociception in murine models (Mishra et al., 2011). In contrast, investigations of human mechanosensitive and mechanoinsensitive nociceptive fibres have revealed that the mechanoinsensitive nociceptive fibres detect both noxious heat stimuli and cowhage itch, but not histaminergic itch (Weinkauf et al., 2015). However, the relationship between heat sensation and histaminergic itch remains obscure. It is suggested that the role of TRPV1 in human itch is different from that in a murine itch. In summary, TRPV1 may be a prospective human therapeutic target for heat-provoked itch (Yun et al., 2011).

Recent reports suggested the importance of calcitonin gene-related peptide (CGRP)-positive sensory neurons in both heat and the itch responses (McCoy et al., 2013; Rogoz et al., 2014). Selective ablation of CGRP alpha primary sensory neurons in mice caused decreased numbers of skin peripheral nerve fibres, impaired responses to noxious heat, and attenuated scratch behaviours induced by histamine or chloroquine (McCoy et al., 2013). Another report investigated the expression level of CGRP in dorsal root ganglia (DRG) derived from mice lacking vesicular glutamate transporter 2 (VGULT2), a transporter of L-glutamate into synaptic vesicles, selectively in TRPV1-positive neurons (*Vglut2*$^{f/f}$;Trpv1-Cre). The results showed increased expression of CGRP mRNA. *Vglut2*$^{f/f}$;Trpv1-Cre mice showed severe scratching behaviour, and this behaviour was significantly reduced by administration of selective CGRP antagonists (Rogoz et al., 2014). These results implied that the heat or itch sensation arises from a complex combination of many kinds of transmitter signals.

From the patients' perspective, both warmth and noxious heat are capable of causing an itch sensation. Pfab et al. found that a repeated, rapid, subtle change in temperature at the skin surface (25 and 32 °C) augmented the histaminergic itch response (Pfab et al., 2010). This suggests that, even with a physiological environmental temperature in our daily life, changes in temperature might augment itch intensity.

Noxious and painful heat or cooling stimuli frequently attenuate the itch sensation. A noxious painful heat stimulus augments the itch response in patients with atopic dermatitis (Table 1). In healthy subjects, a histamine-induced itch can be attenuated by both a painful cool stimulus (around 2–5 °C) and a noxious heat stimulus (45–49 °C) (Fruhstorfer et al., 1986; Yosipovitch et al., 2005, 2007; Ishiuji et al., 2008) (Table 2). However, an itch sensation in subjects with atopic dermatitis was augmented by a noxious heat stimulus, such as at 45–49 °C (Fruhstorfer et al., 1986; Ikoma et al., 2004; Ishiuji et al., 2008), while a painful cool stimulus (5 °C) attenuated the itch (Fruhstorfer et al., 1986) (Table 1). These studies found that the heat stimulus induces and exacerbates itch in patients with atopic dermatitis. This raises the issue that normally, heat does not induce itch (Table 2). Thus, patients with atopic dermatitis suffer from abnormal itching developed by a normally non-itchy stimulus. This abnormal itching is called alloknesis (LaMotte, 1992; Akiyama et al., 2012).

Alloknesis is a sensation that presumably occurs as a result of enhanced itch transmission within the central nervous system, and has been implicated as a

Table 1

	Noxious heat stimulus	Noxious cold stimulus	Reference
Itch without provocation	45 °C: augmented (1/3)	5 °C: attenuated	[18]
	49 °C: augmented	ND	[20]
Histaminergic itch	49 °C: augmented	ND	[19]

Table 2 The impact of both noxious heat and cool stimuli on histaminergic itch in healthy skin.

Noxious heat stimulus	Noxious cold stimulus	Reference
49 °C: attenuated	2 °C: attenuated	[16]
49 °C: attenuated	2 °C: attenuated	[17]
45 °C: attenuated	5 °C: attenuated	[18]
49 °C: attenuated	ND	[19]

ND: not done.

cause of abnormal itching in certain dermatoses. The development of alloknesis varies in accordance with the type of dermatitis. For example, noxious heat or chemical pain stimulation induces itch in atopic dermatitis, but not in psoriasis patients (Ikoma et al., 2004). The pathological mechanism of itch in psoriasis has been identified and is similar to that in atopic dermatitis (Reich and Szepietowski, 2014). Dry skin is more prominent in atopic dermatitis, and may also be involved in alloknesis in atopic dermatitis patients (Akiyama et al., 2012).

Regarding the mechanism of the warmth-provoked itch, it might be included as alloknesis, but the molecular mechanisms remain unknown. Key molecules that cause alloknesis by heat stimuli in atopic dermatitis patients were therefore examined. As skin innervation is mainly observed in dermis, we hypothesized that dermal fibroblasts could be a source of these signal molecules. Thus, we suggest that dermal fibroblast-derived factor might sensitize the peripheral nerve downstream of major pruritogens such as substance P or histamine, which are known to be involved in the pathogenesis of allergic dermatitis.

Herein, we focus in particular on artemin, which is expressed in substance P-treated dermal fibroblasts (Murota et al., 2012). Artemin is a member of the glial cell-derived neurotrophic factor (GDNF)-related family, and acts through a GDNF receptor α3 (GFRα3), leading to peripheral nerve growth or survival. Artemin is not expressed in normal skin and in psoriasis tissues, but accumulates in the upper dermis of lesional skin of both atopic dermatitis and nummular eczema patients (Fig. 1A). *In situ* hybridization for artemin has revealed the expression of artemin mRNA on dermal fibroblasts from atopic dermatitis skin lesions, but not from healthy skin. Peripheral nerve fibre sprouting is frequently observed in lesional skin in atopic dermatitis, and sprouted nerve fibres express GFRα3, a receptor for artemin. These results indicate that artemin has the potential to cause abnormal innervation in skin. Wild-type mice have received intradermal injection with artemin or substance P, and show increased numbers of peripheral nerve fibres and increased intraepidermal neurite outgrowth (Murota et al., 2012).

These results suggest that artemin might affect skin sensations. To explore whether artemin affects cutaneous sensitivity to environmental stimuli, the intensity of perception was evaluated in GFRα3 knockout mice. Although the intensity of mechanosensation in GFRα3 knockout mice is comparable to that in wild-type mice, thermal hypoalgesia is found in GFRα3 knockout mice (Fig. 1B). Moreover, cutaneous administration of artemin induced thermal hyperalgesia (Fig. 1C) (Murota et al., 2012). These results indicated that artemin might regulate thermal sensation of skin via GFRα3. Evidence to support this idea was obtained from the behaviour of artemin-injected mice placed at an environmental temperature of 38 °C. Artemin-injected wild-type mice exhibited grooming of the cheek behaviour (not at the injection site) or of the entire body, in a warm environment, while GFRα3

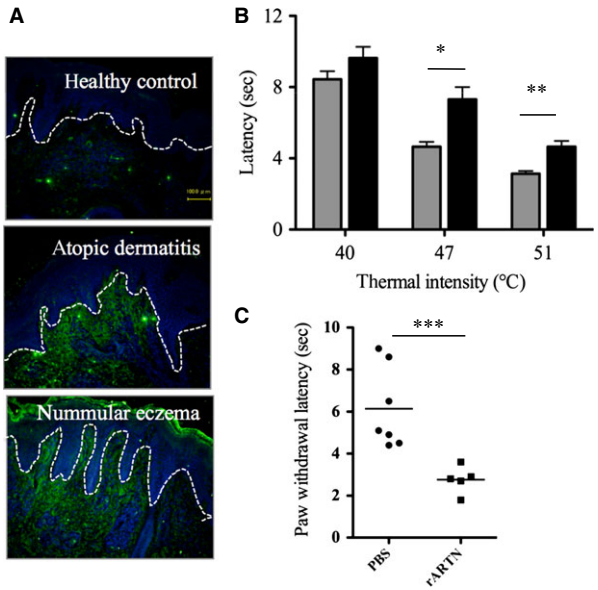

Figure 1 Expression and function of artemin (ARTN) in skin. A: Human skin specimens derived from atopic dermatitis, nummular eczema and healthy skin were immunohistologically stained with artemin antibody (green). The dotted line indicates the junction of the epidermis and dermis (magnification, ×200). B: Response to noxious heat stimuli were measured with the tail flick test. Grey and black bars show wild-type and GFRα3 knockout mice, respectively, $*p < 0.05$, unpaired *t*-test. C: The effect of exogenously administered artemin on thermal hyperalgesia (Hargreaves test) ($n = 5$). $***p < 0.001$, unpaired *t*-test. These figures were reprinted from ref (Murota et al., 2012), with permission.

knockout mice did not show such behaviour (Murota et al., 2012). While there is no direct link between grooming behaviour and pain or itch, these results suggest that accumulation of artemin in peripheral skin may cause discomfort in a warm environment. Future studies examine how artemin causes thermal hyperalgesia. Davis et al. have reported detecting the phenotype of thermal hyperalgesia in transgenic mice that overexpress artemin in skin keratinocytes (K14-ARTN Tg mice), and suggest a possible involvement of TRPV1 in the mechanism of this phenotype (Elitt et al., 2006). However, in our study, administration of the TRPV1-inhibitor capsazepine, fails to inhibit the grooming behaviour in artemin-injected mice given warm treatments (Murota et al., 2012). Based on thermal hyperalgesia from cutaneous artemin administration, and the accumulation of artemin in atopic dermatitis lesions, we speculate that artemin induced thermal hyperalgesia might develop into alloknesis, and might cause warmth-provoked itch in atopic dermatitis. However, relationships between artemin and warmth-provoked itch are speculation, and further studies are needed to clarify this issue.

This mini-review focused on the thermally provoked itch response, and reviewed current research on the clinically relevant mechanisms. As previously discussed in this review, thermally provoked itch is intractable to treatment. Novel therapeutic strategies may result from a better understanding of the mechanism of thermally provoked itch. Research to date indicates that several molecules, including TRPV1, CGRP, VGLUT2 and artemin, might be candidate therapeutic targets for thermally provoked itch therapy.

Author contributions

I.K. and H.M. designed the review and contributed to data collection. H.M. wrote the manuscript.

References

Akiyama, T., Carstens, M.I., Ikoma, A., Cevikbas, F., Steinhoff, M., Carstens, E. (2012). Mouse model of touch-evoked itch (alloknesis). *J Invest Dermatol* 132, 1886–1891.

Elitt, C.M., McIlwrath, S.L., Lawson, J.J., Malin, S.A., Molliver, D.C., Cornuet, P.K., Koerber, H.R., Davis, B.M., Albers, K.M. (2006). Artemin overexpression in skin enhances expression of TRPV1 and TRPA1 in cutaneous sensory neurons and leads to behavioral sensitivity to heat and cold. *J Neurosci* 26, 8578–8587.

Fruhstorfer, H., Hermanns, M., Latzke, L. (1986). The effects of thermal stimulation on clinical and experimental itch. *Pain* 24, 259–269.

Handwerker, H.O. (2014) Itch hypotheses: From pattern to specificity and to population coding. In: *Itch: Mechanisms and Treatment*, Carstens, E, Akiyama, T eds. (Boca Raton FL: CRC Press), NBK200936.

Ikoma, A., Fartasch, M., Heyer, G., Miyachi, Y., Handwerker, H., Schmelz, M. (2004). Painful stimuli evoke itch in patients with chronic pruritus: Central sensitization for itch. *Neurology* 62, 212–217.

Ishiuji, Y., Coghill, R.C., Patel, T.S., Dawn, A., Fountain, J., Oshiro, Y., Yosipovitch, G. (2008). Repetitive scratching and noxious heat do not inhibit histamine-induced itch in atopic dermatitis. *Br J Dermatol* 158, 78–83.

Kim, D.K., Kim, H.J., Sung, K.S., Kim, H., Cho, S.A., Kim, K.M., Lee, C.H., Kim, J.J. (2007). 12(S)-HPETE induces itch-associated scratchings in mice. *Eur J Pharmacol* 554, 30–33.

LaMotte, R. (1992). Subpopulations of nocifensor neurons contributing to pain and allodynia, itch and alloknesis. *AM Pain Soc J* 1, 115–126.

McCoy, E.S., Taylor-Blake, B., Street, S.E., Pribisko, A.L., Zheng, J., Zylka, M.J. (2013). Peptidergic CGRPalpha primary sensory neurons encode heat and itch and tonically suppress sensitivity to cold. *Neuron* 78, 138–151.

Mishra, S.K., Tisel, S.M., Orestes, P., Bhangoo, S.K., Hoon, M.A. (2011). TRPV1-lineage neurons are required for thermal sensation. *EMBO J* 30, 582–593.

Murota, H., Izumi, M., Abd El-Latif, M.I., Nishioka, M., Terao, M., Tani, M., Matsui, S., Sano, S., Katayama, I. (2012). Artemin causes hypersensitivity to warm sensation, mimicking warmth-provoked pruritus in atopic dermatitis. *J Allergy Clin Immunol* 130, 671–682, e674.

Pfab, F., Valet, M., Sprenger, T., Huss-Marp, J., Athanasiadis, G.I., Baurecht, H.J., Konstantinow, A., Zimmer, C., Behrendt, H., Ring, J., Tolle, T.R., Darsow, U. (2010). Temperature modulated histamine-itch in lesional and nonlesional skin in atopic eczema – A combined psychophysical and neuroimaging study. *Allergy* 65, 84–94.

Reich, A and Szepietowski, J.C. (2014) Clinical aspects of itch: Psoriasis. In *Itch: Mechanisms and Treatment*, Carstens, E, Akiyama, T, eds. (Boca Raton, FL: CRC Press), NBK200930.

Rogoz, K., Andersen, H.H., Lagerstrom, M.C., Kullander, K. (2014). Multimodal use of calcitonin gene-related peptide and substance P in itch and acute pain uncovered by the elimination of vesicular glutamate transporter 2 from transient receptor potential cation channel subfamily V member 1 neurons. *J Neurosci* 34, 14055–14068.

Rothman, S. (1941). Physiology of itching. *Physiol Rev* 21, 357–381.

Shim, W.S., Tak, M.H., Lee, M.H., Kim, M., Kim, M., Koo, J.Y., Lee, C.H., Kim, M., Oh, U. (2007). TRPV1 mediates histamine-induced itching via the activation of phospholipase A2 and 12-lipoxygenase. *J Neurosci* 27, 2331–2337.

Stante, M., Hanna, D., Lotti, T. (2005). Itch, pain, and metaesthetic sensation. *Dermatol Ther* 18, 308–313.

Tominaga, M., Caterina, M.J. (2004). Thermosensation and pain. *J Neurobiol* 61, 3–12.

Wahlgren, C.F. (1991). Itch and atopic dermatitis: Clinical and experimental studies. *Acta Derm Venereol Suppl (Stockh)* 165, 1–53.

Weinkauf, B., Dusch, M., van der Ham, J., Benrath, J., Ringkamp, M., Schmelz, M., Rukwied, R. (2015). Mechano-sensitive nociceptors are required to detect heat pain thresholds and cowhage itch in human skin. *Eur J Pain* DOI: 10.1002/ejp.710.

Yosipovitch, G., Fast, K., Bernhard, J.D. (2005). Noxious heat and scratching decrease histamine-induced itch and skin blood flow. *J Invest Dermatol* 125, 1268–1272.

Yosipovitch, G., Duque, M.I., Fast, K., Dawn, A.G., Coghill, R.C. (2007). Scratching and noxious heat stimuli inhibit itch in humans: A psychophysical study. *Br J Dermatol* 156, 629–634.

Yun, J.W., Seo, J.A., Jang, W.H., Koh, H.J., Bae, I.H., Park, Y.H., Lim, K.M. (2011). Antipruritic effects of TRPV1 antagonist in murine atopic dermatitis and itching models. *J Invest Dermatol* 131, 1576–1579.