The effect of escalating heat stimulation on top of anesthetized skin

Riccio, Daniele; Lo Vecchio, Silvia; Arendt-Nielsen, Lars

Published in:
Itch

DOI (link to publication from Publisher):
10.1097/itx.0000000000000065

Publication date:
2023

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

Brief Communication

Itch
International Forum for the Study of Itch

OPEN

The effect of escalating heat stimulation on top of anesthetized skin

Daniele Riccio, PhD[a], Silvia Lo Vecchio, PhD, MSc[a,*], Lars Arendt-Nielsen, PhD, MD[a,b]

Abstract

The relationship between itch and heat pain has been vastly explored. A 70-year-old study, showed the development of paradoxical itch following heat stimulation of anesthetized skin. The aim of this study was to re-evaluate, with more modern technologies and systematic approaches, this paradoxical itch effect. Escalating heat stimuli were applied to the local anesthetized skin of 19 healthy subjects, itch, and pain intensities were continuously assessed during the stimulation. As expected, pain sensation was significantly reduced by local intradermal anesthesia, however, no paradoxical itch sensations were observed for any of the stimulation temperatures.

Keywords: Itch, Pain, Heat, Anesthesia

Itch and pain are 2 different sensations that share many similarities, but to this day, it is not entirely clear how they interact and affect each other. A fundamental understanding of this interaction is crucial for the development of new and better therapies for both sensory modalities.

Many studies have investigated heat pain thresholds (HPT), although the exact temperature threshold can vary a lot depending on the study design and methodology used[1,2], sex[3], and the area stimulated[4]. Moreover, it has been shown that heat pain can modulate (mainly inhibit) itch sensation in various experimental settings[5,6]. The Transient Receptor Potential Vanilloid (TRPVs) are involved in heat transduction and it is known that temperatures above 30 °C can activate TRPV3, TRPV4 by temperature between 30 and 40 °C, and TRPV1 by temperature exceeding 40 °C[7]. TRPVs and various pruriceptors, like histamine receptor[8] and serotonin receptor[9] share a close relationship[10].

A recent study categorized cutaneous sensory nerve endings by their RNA expression[11] and different fiber types involved in either pain or itch were classified. The peptidergic fibers 1 (PEP1) characterized by the expression of substance P are thermosensitive, while the nonpeptidergic fibers (NP) are further divided into 3: NP1 involved in neuropathic pain and itch, NP2 involved in acute itch, for example, histaminergic itch, and NP3 involved in inflammatory itch, for example, serotoninergic itch[11].

Local analgesics (eg, lidocaine) have been known as a potent blocker of the voltage-gated sodium channels (Nav)[12,13] and Nav channels are expressed by all the fibers mentioned above[11]. Hence local analgesics can be used as potent modulators of cutaneous sensory modalities[14,15].

A 70-year-old study by Cormia and Kuykendall[16], investigating histamine effects and interactions in various experimental conditions, showed that heat pain applied on top of anesthetized skin evoked a paradoxical sensation of itch when the anesthesia started to wearing off. This effect has not been validated in later studies using more modern sensory assessment methodologies.

The aim of this study was to analyze evoked itch and pain sensations from cutaneous anesthetized skin using heat pain stimuli of different intensities (Methods, Supplemental Digital Content, http://links.lww.com/ITX/A14).

Results

Pain intensity analysis

In the area treated with saline, the analysis of the pain sensation revealed increasing pain sensation with increasing temperature, in many cases the participants stopped voluntarily the stimulation before the end due to unbearable pain. Furthermore, we observed no difference in pain intensity between saline and lidocaine treatments, when the stimulation applied was in the innocuous range (38–42 °C, **Fig. 1 A**). A significant difference was noted when the temperature was in the painful range (42.2–46 °C) only after 40 minutes from the intradermal injection, showing a decrease in the area under the curve in the lidocaine area

[a]Center for Neuroplasticity and Pain (CNAP), SMI, Department of Health Science and Technology, School of Medicine, Aalborg University and [b]Department of Clinical Gastroenterology, Mech-Sense, Aalborg University Hospital, Aalborg, Denmark

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

*Corresponding author. Address: Center for Neuroplasticity and Pain, Faculty of Medicine, Aalborg University, Fredrik Bajers Vej 7D, D3-217, Aalborg East 9220, Denmark. Tel.: +45 21 39 77 85. E-mail address: slv@hst.aau.dk (S.L. Vecchio).

Itch (2023) 8:e65

Received 25 April 2022; Accepted 21 November 2022

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.itch.com

Published online 10 January 2023

http://dx.doi.org/10.1097/itx.0000000000000065

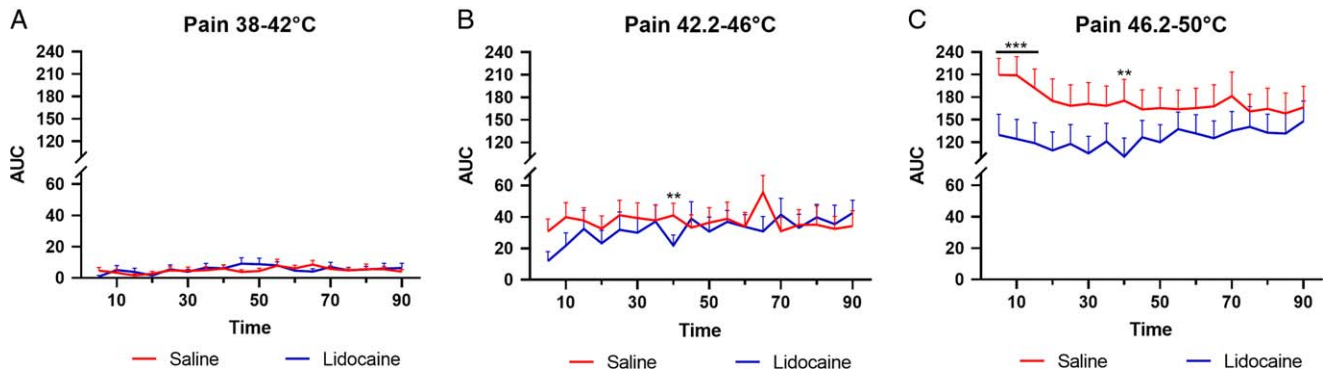

Figure 1. Temporal profiles of pain ratings at different temperature ranges, analyzed as area under the curve (AUC). A, Pain at 38–42 °C; B, 42.2–46 °C; and C, 46.2–50 °C. $^{**}P < 0.01$, $^{***}P < 0.001$. On *x*-axis time expressed as minutes after the treatment, red line saline treatment, blue line lidocaine treatment.

compared with saline area (**Fig. 1 B**). Finally, in the noxious temperature range (46.2–50 °C), there was a significant difference in the pain perception in the first 15 and 40 minutes after the treatment, between the saline and lidocaine intradermal injection (**Fig. 1 C**), showing, as expected, a decrease in area under the curve in the lidocaine area compared with saline area.

Itch intensity analysis

The analysis of the itch sensation revealed a low level of itch perception throughout all the temperature ranges, treatments, and timepoints. Consequently, no statistically significant differences were shown in any of the condition analysed (**Figs. 2 A–C**). These results indicate that the application of an innocuous or noxious thermal stimulus on a previously anaesthetized skin area was unable to evoke a sensation of itch.

Discussion

Decreased pain intensity

As expected intradermally injected lidocaine reduced the thermal pain sensitivity[17]. This effect was specifically observed when the temperature was in the noxious range (46.2–50.0 °C) and in the first 15 minutes following the anesthetization. This data suggests that the analgesic effect induced by lidocaine, after 15 minutes subsided enough to not being able to reduce heat pain perception. A previous study showed how the anesthetic effect developed after lidocaine intradermal injection was present 20 minutes after the injection and absent 120 minutes after[17]. Moreover, Cormia and Kuykendall[16] waited exactly 15 minutes before, as they stated, assessing the paradoxical itch sensation.

In addition, exactly 40 minutes after the treatment with lidocaine it was noticed a lower heat pain perception compared with saline, at the different temperatures' ranges (42.2–46.0 °C, and 46.2–50.0 °C).

Unaltered itch intensity

It has been shown that NP have their terminals in the superficial epidermis while peptidergic fibers' terminals are in the deep epidermis[18,19]. In the present study, intradermal injections of lidocaine were used rather than lidocaine patches in order to attempt blocking only the upper most layers of the dermis. Our hypothesis was that the most superficial NP (itch sensitive) would recover their ability to conduct the signal faster compared with the lower located peptidergic fibers (thermosensitive) leading to paradoxical itch sensation.

Contrarily to the previous study[16], a painful heat stimulation applied on top of local anesthetized skin did not evoke a paradoxical itch sensation in the present controlled study. In this study, 41 °C was used for stimulation which resulted

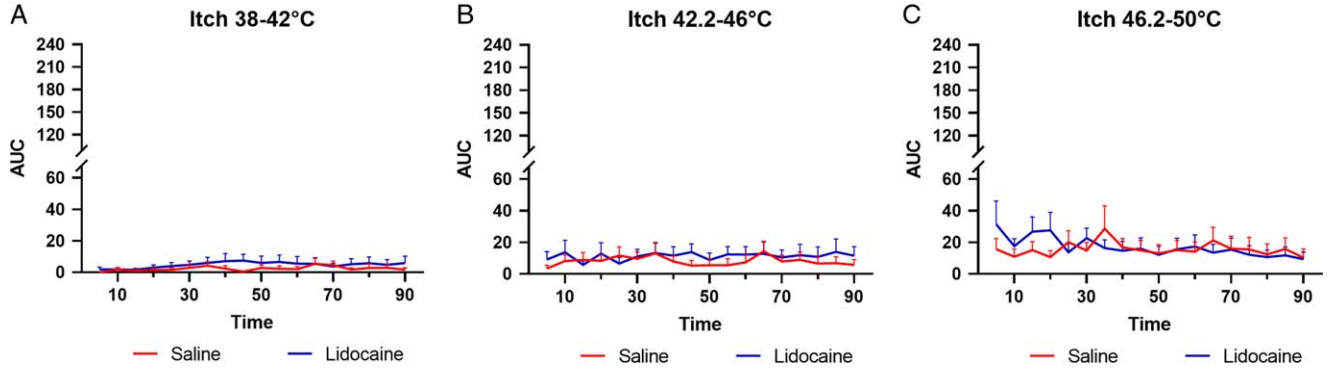

Figure 2. Temporal profiles of itch ratings at different temperature ranges, analyzed as area under the curve (AUC). A, Itch at 38–42 °C; B, 42.2–46 °C; and C, 46.2–50 °C. On *x*-axis time expressed as minutes after the treatment, red line saline treatment, blue line lidocaine treatment.

"in a decided sensation of burning" pain. It could be that this "burning" sensation was characterised as an itch sensation in their set-up.

Intriguingly, it could be that when Cormia and Kuykendall were testing the presence of anesthesia, using pinpricks stimuli, they accidentally evoked alloknesis, leading to believe that they were observing itch sensation. In this study anesthetization was not tested by pinpricks rather it was tested intrinsically by the ramping heat stimuli and the associated pain rating.

Limitations

This study deliberately focusses on a small portion of the original study by Cormia and Kuykendall, while the latter is one of the first and fundamental investigation regarding the effects of histamine. Most of the data reported in that study are still extremely valid (and frequently observed and replicated) to this day. Furthermore, itch was not rated using a VAS scale and thus it was more a qualitative response rather than a quantifiable and measurable response.

Few other considerations can be made. First, although the same experimenter did all the intradermal lidocaine injections it is difficult to ensure the exact same blocking profile across subjects.

Second, the heat ramp hereby used is different from the stimulation used by Cormia and Kuykendall as they used radiant heat to maintain a constant superficial skin temperature at 41° C[16], which is considered below the HPT.

Third, we used lidocaine as opposed to procaine used in the original study. Although, there is a lack of studies comparing the effect of intradermal injection of lidocaine versus procaine, it is known that lidocaine is able to evoke a longer and stronger anesthetization[20]. Therefore, the different anesthetic used in this study may have influenced the recovery capacity of the NP.

Lastly, the study included 2 different VAS scales and concomitant ratings of itch and pain may challenge some volunteers.

Conclusions

No paradoxical itch sensation could be evoked by experimental heat stimuli of increasing intensity when applied to a skin area anesthetized by intradermal injected lidocaine.

Sources of funding

D.R., S.L.V., and L.A.N. are part of the Center for Neuroplasticity and Pain (CNAP), which is supported by the Danish National Research Foundation (DNRF121).

Conflict of interest disclosure

The authors declare that they have no financial conflict of interest with regard to the content of this report.

Acknowledgments

The authors thank Hjalte H. Andersen for his input on the initial discussion of ideas.

References

[1] Lowenstein E, Dallenbach KM. The critical temperatures for heat and for burning heat. Am J Psychol 1930;42:423.
[2] Jones LA, Berris M. The psychophysics of temperature perception and thermal-interface design. Proceedings—10th Symposium on Haptic Interfaces for Virtual Environment and Teleoperator Systems, HAPTICS 2002; 2002:137–42.
[3] Fillingim RB, King CD, Ribeiro-Dasilva MC, *et al*. Sex, gender, and pain: a review of recent clinical and experimental findings. J Pain 2009;10:447.
[4] Park S, Roh SH, Lee JY. Body regional heat pain thresholds using the method of limit and level: a comparative study. Eur J Appl Physiol 2019;119:771–80.
[5] Riccio D, Andersen HH, Arendt-Nielsen L. Antipruritic effects of transient heat stimulation on histaminergic and nonhistaminergic itch. Br J Dermatol 2019;181:786–95.
[6] Yosipovitch G, Duque MI, Fast K, *et al*. Scratching and noxious heat stimuli inhibit itch in humans: a psychophysical study. Br J Dermatol 2007;156:629–34.
[7] Castillo K, Diaz-Franulic I, Canan J, *et al*. Thermally activated TRP channels: molecular sensors for temperature detection. Phys Biol 2018;15:021001.
[8] Shim W-S, Tak M-H, Lee M-H, *et al*. TRPV1 mediates histamine-induced itching via the activation of phospholipase A2 and 12-lipoxygenase. J Neurosci 2007;27:2331–7.
[9] Kim S, Barry DM, Liu XY, *et al*. Facilitation of TRPV4 by TRPV1 is required for itch transmission in some sensory neuron populations. Sci Signal 2016;9:Ra71.
[10] Riccio D, Andersen HH, Arendt-Nielsen L. Mild skin heating evokes warmth hyperknesis selectively for histaminergic and serotoninergic itch in humans. Acta Derm Venereol 2022;102:adv00649.
[11] Usoskin D, Furlan A, Islam S, *et al*. Unbiased classification of sensory neuron types by large-scale single-cell RNA sequencing. Nat Neurosci 2015;18:145–53.
[12] Arcisio-Miranda M, Muroi Y, Chowdhury S, *et al*. Molecular mechanism of allosteric modification of voltage-dependent sodium channels by local anesthetics. J Gen Physiol 2010;136:541–54.
[13] Ahern CA, Payandeh J, Bosmans F, *et al*. The Hitchhiker's guide to the voltage-gated sodium channel galaxy. J Gen Physiol 2016;147:1–24.
[14] Hong J, Buddenkotte J, Berger TG, *et al*. Management of itch in atopic dermatitis. Semin Cutan Med Surg 2011;30:71.
[15] Villamil AG, Bandi JC, Galdame OA, *et al*. Efficacy of lidocaine in the treatment of pruritus in patients with chronic cholestatic liver diseases. Am J Med 2005;118:1160–3.
[16] Cormia FE, Kuykendall V. Experimental histamine pruritus. II. Nature; physical and environmental factors influencing development and severity. J Invest Dermatol 1953;20:429–6.
[17] Atanassoff PG, Brull SJ, Printsev Y, *et al*. The effect of intradermal administration of lidocaine and morphine on the response to thermal stimulation. Anesth Analg 1997;84:1340–3.
[18] Zylka MJ, Rice FL, Anderson DJ. Topographically distinct epidermal nociceptive circuits revealed by axonal tracers targeted to Mrgprd. Neuron 2005;45:17–25.
[19] Lowy DB, Makker PGS, Moalem-Taylor G. Cutaneous neuroimmune interactions in peripheral neuropathic pain states. Front Immunol 2021;12:1064.
[20] Le Truong HH, Girard M, Drolet P, *et al*. Spinal anesthesia: a comparison of procaine and lidocaine. Can J Anesth 2001;48:470–3.