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Received: 14 March 2023 | Revised: 24 July 2023 | Accepted: 19 August 2023

DOI: 10.1002/ejp.2177

EJP European Journal of Pain

ORIGINAL ARTICLE

Electrical matrix stimulation suppresses acute itch independently of activation of sleeping nociceptors

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Funding information
RWTH Aachen University, Grant/Award Number: IZKF TN1-6/IA 532006, IZKF TN1-1IA 532002 and IZKF TN1-1/IA 532001; Research Group Neurosciences; German Federal Ministry of Education and Research/Bundesministerium für Bildung und Forschung, Grant/Award Number: 13GW0334B; German Research Foundation, Grant/Award Number: 368482240, 363055819, LA 2740/3-1, DFG NA 970 3-1 and 397846571

Abstract

Introduction: Itch can be reduced by pain. Activation of sleeping nociceptors (CMi) is a crucial mechanism for the peripheral component of intense and long-lasting pain. Thus, activation of CMi might be especially effective in itch reduction. Electrical stimulation using sinusoidal pulses activates CMi with tolerable pain intensity, whereas short rectangular pulses with low intensity do not. In humans, histaminergic itch is mediated by histamine-sensitive CMi, whereas other pruritogens activate polymodal nociceptors (CM).

Methods: In a psychophysical approach in a balanced crossover repeated-measures design in healthy volunteers, we activated nociceptors by two different electrical stimulation paradigms via a matrix electrode: 4 Hz sinusoidal pulses that activate C-nociceptors including CMi or 4 Hz rectangular stimuli to activate nociceptors excluding CMi. After 5-min stimulation, itch was induced by either histamine iontophoresis or application of cowhage spicules. Itch ratings were assessed via a numerical rating scale (NRS).

Results: Electrical 4 Hz sine wave stimulation (0.1 mA) with low pain ratings of 1.5 (NRS; 0–10) induced an axon reflex erythema (3 cm^2), indicating activation of CMi, whereas rectangular 0.2 ms pulses (average 0.91 mA) with the same pain rating did not. Both electrical stimulation paradigms reduced itch magnitude over time evoked by either histamine or cowhage to a similar extent. Peak maximum itch evoked by histamine was reduced by both stimulation paradigms, but not cowhage maximum itch.

Discussion: Since electrical stimulation with the rectangular pulse paradigm reduces itch to a similar extent as the sine wave stimulation paradigm, the input of CMi is not necessarily required for itch suppression. The input of A-fibres and polymodal nociceptors, similarly, as also achieved by scratching, seems to be sufficient for both forms of chemically evoked itch.

Significance: Since activation of CMi does not provide additional benefit for itch suppression, spinal pain pathways transmitted via CM versus CMi have differential effects on itch-processing circuits. This is important knowledge for using

R. Rolke and B. Namer shared last authorship.

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electrical matrix stimulation as itch suppressor since activation of sleeping nociceptors either requires significantly painful stimulation paradigms or specialized stimulation paradigms as sinusoidal pulses. An alternative approach using half-sine wave pulses with low pain intensity activating specifically polymodal nociceptors to suppress itch via matrix electrode stimulation may be considered.

1 | INTRODUCTION

Chronic itch is a widespread and distressing symptom in the general population with a point prevalence of 13.5% (Matterne et al., 2011). Chronic neuropathic itch or systemic pruritus, for example, in liver or renal failure decreases the quality of life in many patients (Mücke et al., 2016). However, specific mechanism-based treatments are not available for many conditions.

Despite enormous progress in the understanding of molecular pathways of pruritus, the peripheral and central mechanisms by which itch is signalled in humans are still unclear (Schmelz, 2021). Some forms of itch might be mediated by peripheral mediators activating sensory neurons, which are signalling itch. Thus, some forms of chronic itch might have a component of chemically induced itch.

Lysophosphatidic acid (LPA or LPC) in cholestatic liver diseases might be an example for itch partly mediated by chemical activation of peripheral structures (Kremer et al., 2010). In humans, there seem to exist several peripheral pathways for itch: histaminergic itch is mediated by so-called "sleeping nociceptors" (mechano-insensitive nociceptors) (Namer et al., 2008; Schmelz et al., 1997), whereas other pruritogens such as the itch-inducing protease mucunain activate predominantly polymodal (mechano-sensitive) nociceptors (Johanek et al., 2008; Namer et al., 2008). In primates, these two different signalling pathways for itch seem to continue in the spinothalamic tract to the thalamus by activating separate populations of primate spinothalamic tract neurons (Davidson et al., 2007).

In spinal cord, interactions between nociceptive and pruriceptive input leading to a suppression of itch by nociceptive stimuli have been described in detail in mice (Lay & Dong, 2020; Liu et al., 2021; Ross et al., 2010). Nociceptive scratching input following capsaicin injection into the skin enhances activity in the spinothalamic tract neurons, whereas following histamine application, the same scratching stimulus led to reduced activity. Furthermore, it has been demonstrated that capsaicin injections, which are known to elicit prolonged activation of silent nociceptors, are capable of eliminating histamine-induced itch (Brull et al., 1999). This shows not only interaction of nociceptive and pruritic input but also a state-dependent inhibition occurring during/after itch induction (Davidson et al., 2009). However, it remains unclear how these findings in rodents can be translated to humans and integrated into the knowledge about peripheral C-fibres being involved in itch. It is common knowledge that in humans nociceptive input especially via mechano-sensitive afferents during scratching suppresses itch (Cevikbas & Lerner, 2020; Yosipovitch et al., 2007). Other studies showed suppression of itch by different noxious stimuli like heat or mechanical stimuli, but these were astonishingly not effective in itch suppression in patients with atopic dermatitis (Brull et al., 1999; Ishiuji et al., 2008; Yosipovitch et al., 2005). Scratching might induce a vicious scratch–itch cycle and leads to skin damage. Thus, other therapies causing nociceptive input to the spinal cord without those side effects have been thought about. However, the concept "pain suppresses itch" has been used to explore non-pharmacological therapies for itch. In the treatment of pain, electrical stimulation is used since decades, well known as transcutaneous electrical nerve stimulation (TENS). TENS is used as a therapeutic option in chronic pain (Vance et al., 2014), but there is also research on electrical stimulation (Ward et al., 1996) or electro-acupuncture for pruritus (Belgrade et al., 1984; Kesting et al., 2006). Refined electrodes with intracutaneous pins for A-delta and C-fibre stimulation were shown to be effective in reducing experimental itch and chronic itch in patients (Nilsson et al., 1997, 2004). Recently, a matrix electrode, a flat electrode with a 21-pins-cathode surrounded by a ring anode, has been developed that activates transcutaneous superficial nerve fibres of the skin (Mücke et al., 2014). In previous studies, matrix stimulation with low painful intensities reduced both acute and chronic pain (Mücke et al., 2017, 2018) as well as chronic pruritus (Witte et al., 2020). However, it is still unclear, which peripheral nerve fibre populations are needed to provide the crucial input to the spinal cord for optimal suppression of itch.

Sleeping nociceptors also called "mechano-insensitive nociceptors" (CMi) or class 1b nociceptors form a specific peripheral C-fibre class, which is essentially involved in inflammatory pain, neurogenic inflammation, neuropathic pain and central sensitization

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of the nociceptive system. Their activation causes the widespread axon reflex erythema by release of calcitonin gene-related peptide (CGRP) from their huge axonal tree in the skin, which spans many cm^2 (Schmelz et al., 2000). Unfortunately, this nerve fibre class is up to now only functionally characterized in humans by the electrophysiological method of microneurography. Currently, no molecular marker is known for sleeping nociceptor microscopic imaging studies. In mouse, the expression of nicotinic acetylcholine receptor subunit alpha-3 (CHRNA3) characterizes sleeping nociceptors (Prato et al., 2017). However, the axons of these CHRNA3+ dorsal root ganglion neurons only innervate visceral organs and deep tissue layers, not the skin. Apart from the species-dependent difficulty, it remains unclear how human peripheral C-fibres can be compared to the different fibre types in rodents. When comparing rodents and humans, not only fibre properties but also their projections to different spinal cord laminae differ. Hence, it is currently not possible to directly compare spinal nociceptor interaction mechanisms between mice and humans.

In most cases, when pain with peripheral origin evoked by a high-intensity tonic or a chemical stimulus is especially unpleasant, sleeping nociceptors are activated, even if the nature of the stimulus is mechanical, for example prolonged pinch (Schmidt et al., 2000). Also, in clinically relevant pain such as in ongoing peripheral neuropathic pain, the sleeping nociceptors are thought to be the major players, for example, by their spontaneous activity. Thus, activation of sleeping nociceptors should be most effective in suppressing itch according to the principle "pain suppresses itch." For their activation, however, there is the problem that those fibres have higher activation thresholds than other nociceptive C-terminals such as polymodal C-fibres (Rukwied et al., 2020; Weidner et al., 1999). As a result, by using electrical rectangular pulses of high stimulus intensity, most other nociceptors are activated even stronger, and discharge synchronized within this site causing substantial pain. In recent years, it was found that sine wave-shaped electrical stimuli with low amplitude effectively activate C-fibres, including both sleeping and polymodal C-fibres but no A-fibres (Jonas et al., 2018). This enabled us to use electrical sine wave stimulation as a stimulus to activate also sleeping C-nociceptors with tolerable pain. Using this stimulation paradigm, we were now able to elaborate experimentally on the question, if activation of sleeping C-nociceptors is needed or especially effective in suppressing acute chemically induced itch. Additionally, since it is assumed that the interaction between itch and pain takes place at a spinal level, this might shed light on spinal interaction pathways between itch and pain in humans. Most knowledge about these issues has been gained from rodent experiments. However, in mice sleeping C-nociceptors of the skin have not been described with comparable properties to those in humans. Our specific question in the current study was, whether electrical activation of afferent pathways including or excluding sleeping nociceptors modulates itch sensation differentially in humans. A sensitization of itch by electrical sleeping nociceptor activation might be envisaged, since sleeping nociceptors are known for their ability to induce changes in spinal or more central circuits involved in pain or histaminergic itch (Sauerstein et al., 2018). On the other side, sleeping nociceptors are not always active when pain is intense and may thus be effective in itch suppression even with lower electrical stimulus intensities.

We used a crossover design of inducing acute pruritus via two different signalling pathways, the histaminergic itch via sleeping nociceptors and the non-histaminergic itch via polymodal fibres, and explored two different adjacent electrical stimulation paradigms (rectangular versus sinusoidal pulses) activating either A- and C-fibres excluding sleeping nociceptors or C-fibres including sleeping nociceptors. Thus, we explored a potential differential interaction between pathways including or excluding sleeping nociceptors from both sides: algogenic and pruritic.

2 | METHODS

2.1 | Participants

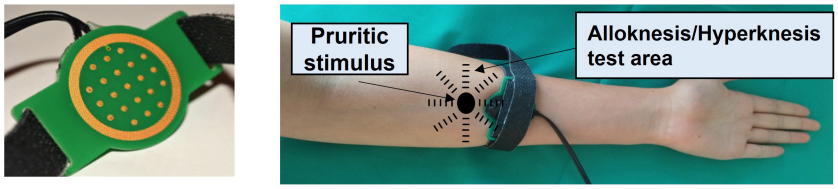
A total of 18 female volunteers were recruited at RWTH University. To exclude sex differences in itch perception (Hartmann et al., 2015), all subjects were female (age 23.5 ± 3.48 years, MW ± SD; range 18–29). None of the participants suffered from allergies, neurological, dermatological or any other chronic diseases. None of the participants used anti-histaminergic local or systemic treatments. Two volunteers were excluded after the training session, because of insufficient itch ratings (<2 numerical rating scale [NRS]; 0–10) to the test stimulus cowhage. The study was approved by the local ethics committee. All participants gave written informed consent and could withdraw from the experiment at any time.

2.2 | Matrix electrode

Stimulation was performed with a matrix electrode, which produces an 3D-multicentric electrical field (Mücke et al., 2014, 2017). The electrode consists of 21 needle-like pins as cathode, which are all together surrounded by one flat concentric ring anode (Figure 1a). The contact points are arranged in five rows and five

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(a)



(b)

Histamine + rectangular	Cowhage + sham	Cowhage + rectangular	Histamine + sine wave	Histamine + sham	Cowhage + sine wave
Group 1	Group 6	Group 5	Group 4	Group 3	Group 2
Group 2	Group 1	Group 6	Group 5	Group 4	Group 3
Group 3	Group 2	Group 1	Group 6	Group 5	Group 4
Group 4	Group 3	Group 2	Group 1	Group 6	Group 5
Group 5	Group 4	Group 3	Group 2	Group 1	Group 6
Group 6	Group 5	Group 4	Group 3	Group 2	Group 1

FIGURE 1 (a) Matrix stimulation electrode and site of stimulation (volar forearm). Testing for alloknesis/hyperknesis was performed after removal of the matrix electrode when the initial pruritogen-induced itching sensation had subsided. Panel (b) Shows the balanced order of chemical pruritogens and the type of electrical stimulation following the arrows for each test group (each group with $N = 3$). Two subjects were excluded due to insufficient itch ratings in the training session, making the total number of subjects ($N = 16$).

columns and had a distance of 0.4 mm. All pins were stimulated simultaneously. The stimulation area was at the volar forearm. Electrical stimuli were produced by a constant current source (Digitimer DS5 or Digitimer DS7; Digitimer Lgt) and controlled by a trigger unit (Universal-Pulse Generator or via the computerized system DAPSYS).

2.3 | Stimulation paradigms

Electrical stimulation was performed with 4 Hz sinusoidal pulses, corresponding to 250 ms for one complete sine wave cycle (Jonas et al., 2018) and 4 Hz rectangular pulses of 200 μs width (Mücke et al., 2018). In each session, individual perception and pain threshold for every subject were determined three times. Current density was slowly increased (0.1 mA/s for rectangular pulses and 0.005 mA/s for sine wave pulses) starting at 0 mA. The subjects should verbally indicate individual perception, pain threshold and NRS 1.5 value (NRS, 0="no sensation," 1 = "pain threshold" and 10 = "most intense pain imaginable") and for our validation protocol NRS 5. We assessed the NRS in 0.5 rating point steps. For the following 5 min, we used an electrical stimulation intensity, which corresponds to NRS 1.5 corresponding to a value slightly above pain threshold.

2.4 | Pruritic stimuli

For histaminergic itch induction, histamine 1% in distilled water was applied on the ventral forearm via iontophoresis (20 ms, 1 mA) 1 cm proximal of the matrix electrode. To produce non-histaminergic itch, 10–20 cowhage spicules from a cowhage bean were inserted into the skin with a tweezer and rubbed in an area of 1-cm-diameter proximal to the matrix electrode. After 5 min of itch rating or in case of prolonged itch after the end of itch stimulation, the spicules were removed from application site with an adhesive tape.

To examine itch intensity, subjects rated their sensation verbally on a NRS from 0 to 10 every 10 s (NRS 0 = "no sensation"; 1 = "the slightest itch sensation; itch perception threshold"; 3 = "impulse to scratch"; 10 = "most intense itch imaginable").

2.5 | Testing for alloknesis and hyperknesis

When itch sensation subsided, alloknesis and hyperknesis were tested following removal of the matrix electrode. Alloknesis was specified as an itch perception after a light touch stimulus with a brush that would normally not produce any itchy sensation. Hyperknesis was determined as enhanced itch after a slightly painful stimulus (toothpick). Areas of alloknesis/hyperknesis were mapped after removing the matrix electrode by five short stimuli at intervals of 1 cm on a circular pattern in eight directions moving from outside towards the pruritogen application area. An alloknesis/hyperknesis area was defined as the presence of alloknesis/hyperknesis perception in an area beyond 0.5 cm around the pruritogen application site in all directions (LaMotte et al., 2009).

2.6 | Assessment of axon reflex erythema

Blood flow measurements were performed by a full-field Laser Perfusion Imager (moorFLPI-2; Moor

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Instruments). The scanned field was proximal of the matrix electrode on the volar forearm. Scan mode was temporal processing 4 s per image. Images were scanned three times: before stimulation, after 4 min stimulation and after 1 min itch. The offline baseline image was subtracted from the other images. Increased blood flow was defined as a perfusion value of a pixel 2 standard deviations above the baseline and summarized as an area including all these pixels.

2.7 | Validation protocol for matrix stimulation

We used laser speckle imaging to image a possible axon reflex erythema spreading around the stimulation site. Widespread axon reflex erythema is generated by neuropeptide release by activated CMi fibres and can be used as indirect indicator of CMi activation. During 5 min of matrix stimulation, three laser speckle images were performed every full minute and values averaged for evaluation. This was repeated for three conditions: sine wave stimulation at pain threshold, rectangular stimulation at pain threshold and rectangular stimulation at pain intensity of NRS 5 to show that rectangular stimulation can activate CMi fibres using higher current amplitudes. A widespread erythema outside and around the stimulation side has been shown to be dependent on action potential conduction in the terminal tree of sleeping nociceptors in the skin (Schmelz et al., 2000).

2.8 | Experimental protocol

The participants familiarized in a training session with the electrical and chemical stimulation rating procedures. The training session took place between 48 h and 4 days before the first test session. The experimental protocol consists of six experimental sessions with a minimum of 48 h of interval in between them. Each experimental session started with 5 min of matrix stimulation followed by the application of the pruritogen and alloknesis/hyperknesis testing. Skin blood flow was tested using laser speckle imaging before and after matrix stimulation and 1 min after application of the respective pruritogen. Electrical matrix stimulation was performed using two different stimulation paradigms, sinusoidal pulses or rectangular pulses, and as control condition sham stimulation with 0 mA. The subjects were told, and they would get two stimulation paradigms which they would feel and one stimulation paradigm in which the intensity is below perception threshold. Itch application consisted of histamine iontophoresis or cowhage spicule application. The order of experimental conditions was completely balanced across six subject groups, each group starting with a different condition (Figure 1).

2.9 | Statistics

All data were analysed using Statistica 7.1 software (StatSoft). Differences between the testing conditions (no stimulation vs. sine wave stimulation vs. rectangular pulse stimulation) or between histamine and cowhage were tested by repeated-measurements analysis of variance (ANOVA). For testing differences between factors, we used post hoc Fisher's least square difference (LSD) test. Significant differences were assumed at a p value below 5%. For analysis of alloknesis and hyperknesis change, we used a non-parametric chi-square test (2×2 table) with significant differences at a p value below 5%.

3 | RESULTS

3.1 | Conditioning electrical matrix stimulation with sine wave pulses induced axon reflex flares

Increases of applied current every minute by 0.02 mA for sine wave and 0.2 mA for rectangular pulses were found to be suitable to keep the desired NRS of 1.5–2 constant over 5 min.

Sine wave stimulation evoked a widespread axon reflex erythema around the matrix electrode of $3.52 \pm 0.17\,cm^2$, which was significantly larger than the small skin reddening directly at the edge of the matrix electrode evoked by rectangular pulse stimulation of $0.91 \pm 0.07\,cm^2$ ($p < 0.01$; LSD post hoc test) ($F = 5.65$; $p < 0.05$; repeated-measurements ANOVA). Both stimulation paradigms were rated similarly painful (NRS ~1.5 to 2 out of 10).

To test whether rectangular wave pulses with higher intensities also elicit axon reflex erythema with the matrix electrode, we additionally used stimulation intensities rated NRS 5 out of 10. The mean stimulation intensity of 3.14 ± 0.61 mA was rated NRS 5 out of 10. With this current intensity, an axon reflex erythema of $2.01 \pm 0.24\,cm^2$ was elicited around the stimulating electrode (Figure 2).

In the sham stimulation paradigm, there was no significant difference in itch ratings between both histamine and cowhage stimulation ($F = 0.36$; $p = 0.56$; repeated-measurements ANOVA; Figure 3a).

Both pruritogens evoked itchy sensations with a maximum itch rating of NRS 4.5 ± 0.1 (histamine) and $4.6 + 0.1$

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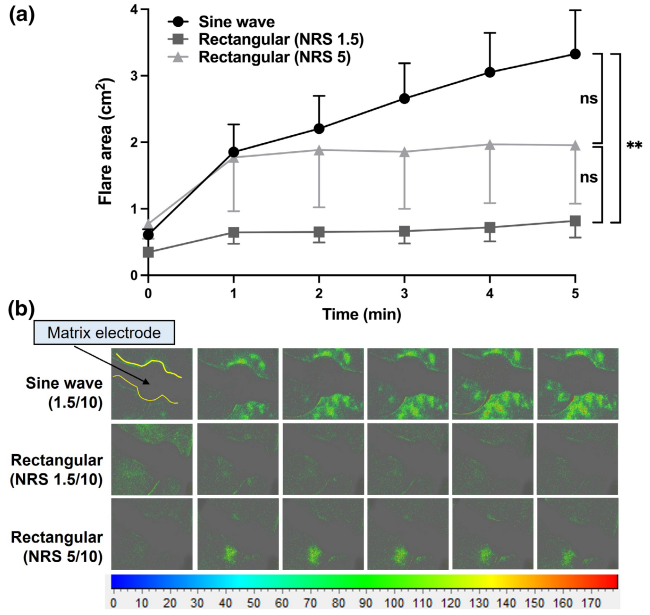


FIGURE 2 Flare areas under electrical stimulation using the matrix electrode. (a) Flare areas (cm^2) comparing electrical sine wave stimulation versus rectangular pulse stimulation titrated to pain ratings of 1.5 or 5 out of 10 numerical rating scale (NRS). (b) Full-field Laser Perfusion Imager Specimen for sine wave (upper row) and rectangular stimulation (middle row rating 1.5%/10, lower row rating 5/10). Stars denote level of significance; $^{**}p < 0.01$; ns = not significant.

(cowhage), respectively (Figure 3b,e). Cumulative itch ratings (NRS, recorded every 10 s) over 5 min were in a similar range with 94.8 ± 2.4 for histamine and 86.3 ± 3.0 for cowhage (Figure 3c,f). Histaminergic itch had a different time course by lasting longer than cowhage itch (mean rating >1 for histamine 517 ± 20.9 s, for cowhage 302.7 ± 7.4 s [$F = 7.44$; $p < 0.05$; repeated-measurements ANOVA]; Figure 3a,d).

For testing the effect of matrix stimulation on chemically induced itch sensations, we used a similar individualized pain rating based on a stimulation paradigm with rising stimulation intensities as in the first experimental series. Mean current intensities were tailored corresponding to a pain perception rated NRS 1.5 out of 10. At the beginning of the stimulation period, current intensities for sine wave stimulation were 0.18 ± 0.03 mA (mean ± SEM; range 0.04–0.58 mA) and for rectangular stimulation 2.45 ± 0.35 mA (mean ± SEM; range 0.7–5.4 mA).

Electrical matrix stimulation reduced cumulative itch ratings of both types of itch upon histamine and cowhage. This finding was independent of the conditioning electrical stimulation paradigms, sine wave or rectangular-shaped pulse forms in contrast to sham stimulation ($F = 10.7$; $p < 0.001$; repeated-measurements ANOVA; Figure 3c,f). In detail, rectangular stimulation reduced

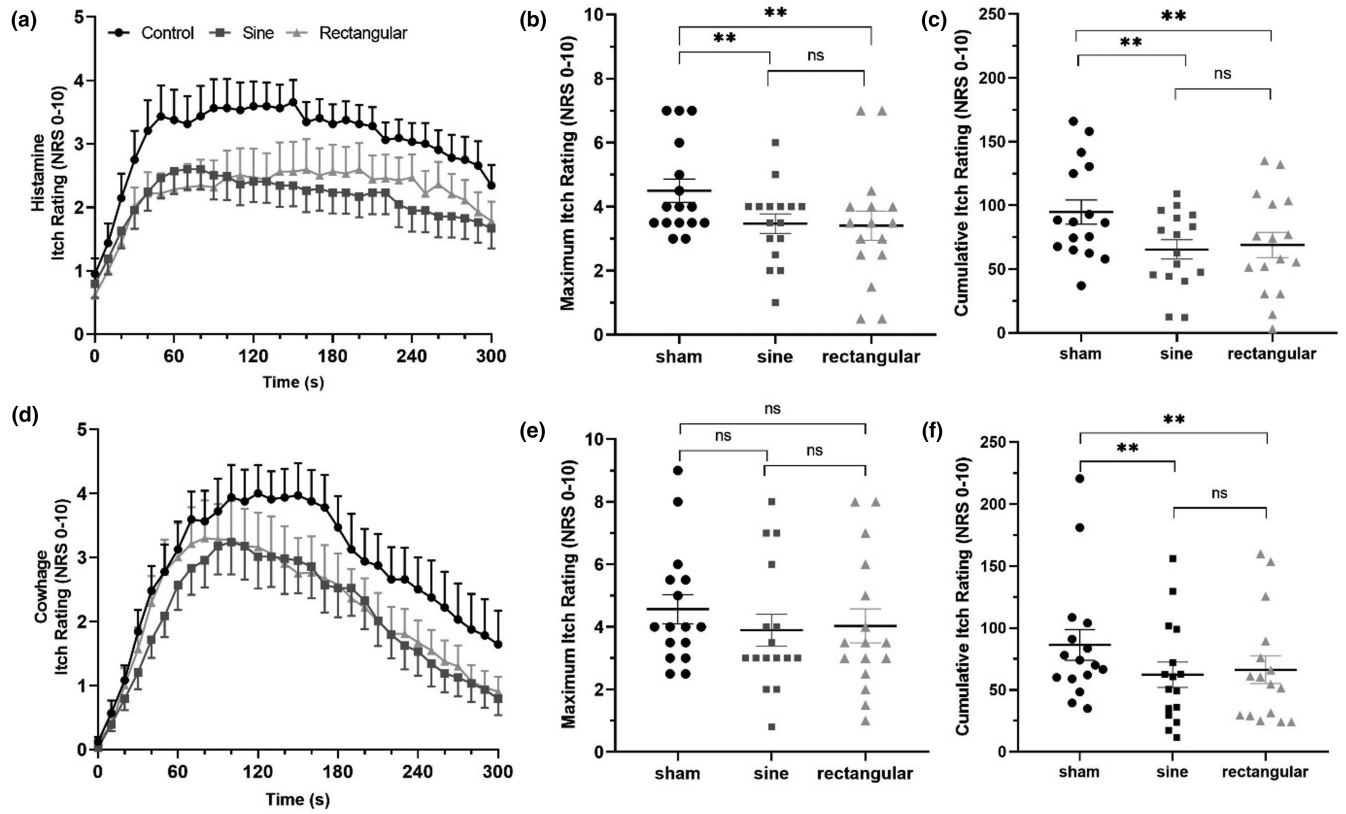


FIGURE 3 Suppression of itch intensity ratings after histamine (a–c) or cowhage (d–f) due to sine wave or rectangular electrical matrix stimulation. Matrix stimulation significantly reduced itch after histamine or cowhage independent from the type of electrical stimulation. Stars denote level of significance; $^{**}p < 0.01$; ns = not significant.

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cumulative ratings of histaminergic itch from 94.8 ± 2.4 to 68.9 ± 2.5 ($p < 0.01$; LSD post hoc test) and cowhage itch from 86.3 ± 3.1 to 66.3 ± 2.8 ($p < 0.01$; LSD post hoc test).

Maximum itch evoked by histamine was significantly reduced from NRS 4.5 ± 0.1 to 3.4 ± 0.1 ($p < 0.01$; LSD post hoc test) (Figure 3b). However, the maximum itch intensity evoked by cowhage was not significantly changed by rectangular stimulation (NRS 4.6 ± 0.1 to 4.0 ± 0.1 [$F = 0.87$; $p = 0.87$; ANOVA]) (Figure 3e).

When comparing the effect of the stimulation paradigms on the two pruritogens, no significant difference was found ($F = 0.36$, $p = 0.56$; ANOVA). This shows that itch evoked by the two pruritogens was reduced independently of the electrical waveforms. Mean maximum itch induced by histamine was reduced by 1 NRS rating point, whereas cowhage itch maximal rating was reduced by 0.5 rating points.

Sine wave stimulation alone resulted in an axon reflex erythema spreading around the matrix electrode with a size of 3.15 ± 0.14 cm^2 exceeding the area covered by the matrix electrode (Figure 2b). In contrast, rectangular stimulation evoked skin reddening of only 1.43 ± 0.96 cm^2 directly around the electrode, which has a circumference of 11 cm ($F = 23.5$; $p < 0.001$; repeated-measurements ANOVA followed by LSD post hoc tests comparing sham vs. sine wave [$p < 0.001$], sham vs. rectangular [$p < 0.05$], sine wave vs. rectangular [$p < 0.001$]).

3.2 | Chemically induced axon reflex erythema is not altered by electrical stimulation

As shown before, histamine produces an axon reflex erythema, whereas cowhage does not (Johanek et al., 2007). Electrical sine wave stimulation induced a small-sized axon reflex erythema around the matrix stimulator, whereas stimulation with rectangular-shaped pulses does not. However, the size of the histamine-induced axon reflex erythema is not altered by prior matrix stimulation by either stimulation paradigm (Figure 4).

3.3 | Alloknesis

Only few volunteers developed alloknesis (3–8 of 16 subjects over all conditions) or hyperknesis (2–6 of 16 subjects). A chi-square test showed no significant differences for the probability of occurrence of alloknesis or hyperknesis with or without electrical stimulation. As only very few volunteers suffered from altered alloknesis or hyperknesis, no further statistical analyses of the area of hyperknesis or alloknesis were performed.

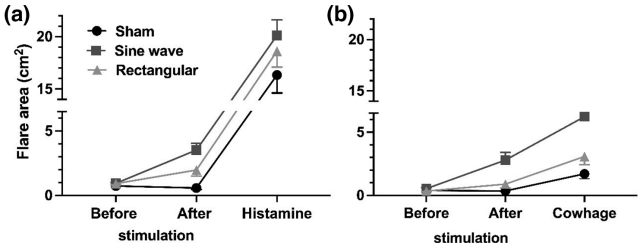


FIGURE 4 Flare areas (cm^2) under electrical stimulation using the matrix electrode plus additional histamine or cowhage. (a) Histamine and (b) cowhage flare areas comparing electrical sine wave stimulation versus rectangular pulse stimulation. Stars denote levels of significance; ns = not significant.

4 | DISCUSSION

Here, we show that preceding electrical matrix stimulation reduced both histaminergic and non-histaminergic itch evoked by cowhage spicules independently of sleeping nociceptor activation. Electrical stimulation has been explored in its potency over decades to modulate itch and pain (Klein et al., 2004; Mücke et al., 2014; Nilsson et al., 2004; Witte et al., 2020). The studies revealed both sensitization and desensitization upon electrical stimulation. In the clinical context, a reduction of itch upon a non-pharmacological treatment option would be looked-for, whereas for research sensitization protocols for the development of experimental human models of chronic itch would be desirable.

Interactions between electrical stimulation and itch perception might occur on different levels of the somatosensory system: primary afferents, spinal cord or brain. Peripheral nerve fibres are modulated in their conductive properties by electrical stimulation and thus modulate the transmission of information about itch-inducing stimuli to the spinal cord. For example, when peripheral afferent nerve fibres transmit a higher amount of action potentials, the activation thresholds increase and chemically induced action potentials might not be generated or conducted anymore (Uebner et al., 2014). On the other hand, activity induced by electrical stimulation might accommodate the axons so that phenomena as supernormal phases take place leading to higher discharge frequencies at the spinal cord (Weidner et al., 2002). However, in our experiments, several reasons speak against a peripheral place of action: (1) The axon reflex erythema evoked by histamine was not altered by electrical stimulation indicating unchanged action potential conduction properties in the axonal trees of those nerve fibres transmitting information about histaminergic itch. (2) Itch mediators were applied proximally of the electrode. Thus, many axons activated by cowhage, which have a small terminal tree,

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were not previously activated by the heterotopic matrix stimulation. (3) The nerve fibre classes activated by rectangular electrical pulses with the here used pulse width, and intensity is different from the nerve fibre class transmitting histaminergic itch. Histamine-sensitive sleeping nociceptors require much higher rectangular currents for activation as shown by the lacking axon reflex erythema with stimulation intensities at NRS 1.5 out of 10. It might be that very few sleeping nociceptors are activated, since they can basically induce secondary mechanical hyperalgesia without an axon reflex erythema (Sauerstein et al., 2018). However, in this study, a very high stimulation intensity and a very low stimulation frequency of 1/20 Hz were used resulting in a pain rating of 6 out of 10. The action potential frequency of 1/20 Hz is too low to result in a relevant accumulation of the vasodilatory substance CGRP released from sleeping nociceptors to induce an axon reflex erythema (Schmelz et al., 2000). However, the synchronized input to the spinal cord via many fibres that are activated by the high current intensity is highly effective in causing spinal sensitization. Additionally the low stimulation frequency prevents adaptation of the nerve fibres. We used in our study lower current intensities for stimulation resulting in pain ratings of approx. 1.5 out of 10 despite the use of higher frequencies (4 Hz). Thus, it is very unlikely that with our stimulation paradigm, sleeping nociceptors are activated sufficiently to induce spinal sensitization. However, rectangular pulses with NRS 1.5 intensity were similarly effective in reducing histaminergic itch as sine wave pulses, additionally supporting the concept that the main effect of itch reduction is not taking place at the level of the primary afferents. Taken together, we therefore assume that the itch-suppressing effect of the conditioning matrix stimulation is mainly located in the spinal cord dorsal horn and/or in the brain. Most likely, "wide-dynamic-range" first-order sensory projection neurons to the thalamus play an important role here as they also process pain and are susceptible to neuromodulation because they can change their activity level upon low- or high-frequency electrical stimulation (Mücke et al., 2014). At spinal level, complex interactions between pruritic and nociceptive inputs have been described in animals in details (Bliss & Cooke, 2011; Chen, 2021; Chen & Sun, 2020). Those highly complex interactions, when put into one sentence, follow the rule "pain suppresses itch." And within this, interaction especially mechanical input like scratching is highly effective in itch reduction. However, scratching is no suitable remedy in chronic itch since repeated scratching damages the skin resulting in chronic structural changes of the skin and a vicious itch/scratch cycle can be generated (Mack & Kim, 2018). In human beings, spinal circuits cannot be scrutinized directly as compared to animals and thus remain up to now a kind of "black box." Different indirect measures using high- or low-frequency electrical sensory input are used to gain information about human spinal/central circuits modulating pain or itch (Klein et al., 2004, 2006). Both phenomena of long-term depression and long-term potentiation in the nociceptive system, as described in animals, might underly those effects of reduced or increased pain/itch sensation, respectively (Klein et al., 2004, 2006, 2007; Nilsson et al., 1997, 2004).

We assessed with our experimental paradigm, if there is any interaction between the two peripheral pathways transmitting itch and the two different pathways transmitting pain. Our specific question was, whether electrical activation of two different afferent pathways including or excluding sleeping nociceptors modulates itch sensation mediated by either sleeping nociceptors or polymodal nociceptors differentially in humans? Sleeping nociceptors play a crucial role in spinal modulation in the form of generation and maintenance of hyperalgesia. Already low-frequency input via these nerve fibres can cause spinal sensitization resulting in mechanical hyperalgesia (Sauerstein et al., 2018). Electrical stimulation can cause both sensitization and desensitization depending on stimulation frequency and activated sensory nerve fibre populations (Klein et al., 2004; Nickel et al., 2011). We could demonstrate upon the presence of an axon reflex erythema that we activate with sine wave-shaped electrical pulse forms the class of sleeping C-nociceptors in addition to polymodal C-fibres also with the special configuration of the matrix electrode (Schmelz et al., 2000). Short rectangular pulses (evoking the same pain rating) induced no widespread axon reflex erythema. The lacking axon reflex erythema in combination with the fact that we stimulate with a low current intensity below the activation threshold of sleeping nociceptors indicates that sleeping C-nociceptors were not significantly activated. Our two-itch paradigm activates two different peripheral pathways: histamine activates the sleeping C-nociceptors, whereas cowhage activates polymodal nociceptors (Namer et al., 2008). Thus, we used a balanced crossover design of pathways including or excluding sleeping C-nociceptors for itch induction and electrical modulation. Preceding conditioning electrical matrix stimulation reduced the percept of itch independently of the activated pruritic pathway. Thus, both forms of itch, histaminergic itch via sleeping C-nociceptors and non-histaminergic itch via polymodal nociceptors (cowhage), are reduced by activation of other peripheral nerve fibres than sleeping nociceptors.

Scratching the skin is the first reaction to explore relief from itch. Scratching is most effective and satisfying when performed with sharp edges such as fingernails.

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Teleologically seen, these movements with sharp edges remove the itchy agent before it causes further damage or enters deeper into the skin. This type of scratching stimulus activates mechano-sensitive A-fibres and very effectively mechano-sensitive C-fibres. Mechano-sensitive C-fibres form the fibre population, which is activated by electrical matrix stimulation using either pulse forms, sine wave or rectangular. Sleeping nociceptors are properly located in deeper skin layers (Sauerstein et al., 2018) and are mechano-insensitive in their native condition. Thus, they are not activated by scratching. We therefore hypothesize that the nociceptive input of sleeping C-nociceptors to the spinal cord has a different connectivity to the itch pathways within the spinal cord compared to mechano-sensitive nociceptors. It must be kept in mind that there are two different subpopulations of sleeping C-nociceptors. Those sleeping C-nociceptors that discharge over long time and strongly to histamine stimulation form a specific subclass of sleeping C-nociceptors (Schmelz et al., 1997). They are characterized by lower conduction velocity, larger receptive fields and less responsiveness to chemical stimuli causing pain (Schmelz et al., 2003). In our study, we activated the histamine-responsive sleeping C-nociceptor subclass with histamine, whereas it remains unclear whether a particular subpopulation or all classes of sleeping nociceptors are activated by electrical sine wave stimulation. However, very little is known about spinal pathways of sleeping C-nociceptors in humans, preventing further interpretation.

There might be also involvement of other sensory fibre classes in itch suppression such as C-tactile or A-fibres (Sakai et al., 2020). In a human study using selective A-fibre nerve block, the scratch-induced itch relieve was unchanged during A-fibre blockade. This suggests that A-fibres are not required for itch relieve by scratching (Mochizuki et al., 2017). Our study also supports this conclusion. Because A-delta fibres are not activated by sinusoidal wave stimuli at the intensity we used, we conclude that their activation is not an absolute requirement for itch reduction but could also contribute to itch suppression by other stimuli. There is evidence that C-tactile fibres are activated also by sinusoidal wave stimulation (Jonas et al., 2018), but human microneurographic and pig single nerve fibre studies suggest that they are activated by square-wave pulses particularly in the intensity range we used herein. Therefore, we cannot draw any conclusions about the influence of C-tactile fibres on itch suppression.

4.1 | Clinical implications

Although chronic itch as seen, that is in atopic dermatitis, is pathomechanistically different from acute itch as evoked in our study with histamine or cowhage, we would like to discuss potential clinical implications here as some forms of chronic itch might have a peripheral chemical component. In cholestatic itch, an accumulation of LPA was correlated with itch intensity (Kremer et al., 2010) and there might be activation of pruriceptors by LPA or other substances accumulating during cholestasis such as steroids acting as GABA receptor modulators. We demonstrated that LPA activates peripheral nociceptors in humans (Düll et al., 2022). Recently, it has been shown that chloride ions play an important role in non-histaminergic itch (Kim et al., 2022), so that also ionic alterations might play a role in chronic itch. In diseases associated with pruritus, such endogenous metabolites or ionic alterations might act differently to subclinically altered peripheral nociceptor performance with the result of ongoing discharges in peripheral sensory nerve fibres. Those ongoing discharges could result in itch sensation when the right population of neurons is active with appropriate discharge patterns.

There have been several attempts to relieve itch by electrical stimulation (Nilsson et al., 2004). Disadvantages of prior invasive attempts include electrodes that had to be inserted into the skin. The design of the matrix electrode as used in the current study allows the preferential distribution of electricity across superficial epidermal skin layers where unmyelinated nerve fibre endings of A-delta or C-fibres can be found. This matrix stimulation paradigm was effective in relieving itch without skin penetration. The amount of electrical current intensity to reach such itch reduction was very low and well within the range that TENS machines might offer using conventional batteries. Moreover, the involvement of sleeping nociceptors, which have a much higher electrical activation threshold with rectangular pulses causing more pain, was not necessary to achieve an itch-reducing effect. Another positive effect of not activating sleeping nociceptors is that the risk of central sensitization leading to hyperalgesia or allodynia is reduced. This reduction in central sensitization and the associated clinical phenomena, such as hyperalgesia or allodynia, appears even more likely due to the absence of significant activation of CMi (characterized by the absence of axon reflex erythema) following the application of rectangular low-intensity stimulation commonly employed in clinical settings, particularly when applied repeatedly. Central pruritogenic sensitization on a spinal cord level is thought to be a component of chronic itch in patients, too. Here, a functional "rewiring" of spinal processing via matrix stimulation might have beneficial effects in chronic itch (Nilsson et al., 2004; Witte et al., 2020). In further studies, the relatively specific and very effective activation of mechano-sensitive polymodal nociceptors by slowly depolarizing half-sine wave stimuli (Rukwied et al., 2020)

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should be explored in their potency to reduce itch. These pulses evoke a burst of action potentials and might mimic the nociceptor discharges in mechano-sensitive nociceptors as evoked by scratching but without skin damage. In combination with a larger matrix electrode that covers a larger skin area and thus causes more spatial summation, this approach might be a more effective tool for itch reduction in pathologic conditions.

AUTHOR CONTRIBUTIONS

M. Schwarzenauer performed the experiments, analysed the data, wrote the manuscript and created the figures. B. Namer and R. Rolke designed the study, contributed to data analyses, statistics and interpretation. R. Rolke, R. M. Rukwied, A. Lampert and B. Namer discussed the results and critically revised the manuscript. All authors discussed and interpreted the results and commented on the manuscript.

ACKNOWLEDGEMENTS

We are indebted to all volunteers for their consent and study participation.

FUNDING INFORMATION

AL, RR and BN are supported by a grant from the Interdisciplinary Center for Clinical Research within the Faculty of Medicine at the RWTH Aachen University (IZKF TN1-1/IA 532001, IZKF TN1-1IA 532002 and IZKF TN1-6/IA 532006) and BN by funding of the Research Group Neurosciences. AL and RR are funded by the BMBF consortium "Bio2Treat" (German Federal Ministry of Education and Research/Bundesministerium für Bildung und Forschung, BMBF, "Chronische Schmerzen – Innovative medizintechnische Lösungen zur Verbesserung von Prävention, Diagnostik und Therapie," number 13GW0334B). RMR, BN and AL are supported by grants from the German Research Foundation DFG (397846571 [RMR], FOR 2690 Project 3 [RMR], and Project 7 [BN], DFG NA 970 3-1, LA 2740/3-1, 363055819/GRK2415 Mechanobiology of 3D epithelial tissues [ME3T], 368482240/GRK2416, MultiSenses-MultiScales).

CONFLICT OF INTEREST STATEMENT

The authors report no conflict of interests towards the content of this work. AL has received counselling fees from Grünenthal and has a research contract with Grünenthal and Hoffmann La Roche. RR has received fees as a speaker or for counselling services from the following companies: Aristo Pharma, Cannamedical, Hormosan, Grünenthal, Lilly & Company, Pfizer, Tilray, Spectrum Therapeutics.

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How to cite this article: Schwarzenauer, M., Rukwied, R. M., Lampert, A., Rolke, R., & Namer, B. (2024). Electrical matrix stimulation suppresses acute itch independently of activation of sleeping nociceptors. *European Journal of Pain*, *28*, 285–296. https://doi.org/10.1002/ejp.2177

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