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Original experimental

Discriminative sensory characteristics of the lateral femoral cutaneous nerve after mepivacaine-induced block

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HIGHLIGHTS

- QST allows differential testing of low threshold mechanosensitive units and different nociceptor classes.
- Differential sensitivity of nociceptors and non-nociceptors to peripheral nerve block was investigated.
- Higher concentrations of mepivacaine were required to maintain analgesic effects for 3 h.
- Test stimuli can be optimized to investigate different nociceptor classes.
- Suprathreshold response characteristics of nociceptors might help to design more specific (local) analgesics in the future.

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This work is dedicated to Otto von Krusenstierna, Kungliga Tekniska högskolan, Stockholm, Sweden, a warm-hearted enthusiastic scientist for decennia.

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Nociceptive C-fibres
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ABSTRACT

Background and objectives: Unmyelinated C-fibres comprise the largest group of somatic afferents and have demonstrated a crucial role not only in the perception of high-threshold mechanically, thermally or chemically induced pain, but also in non-harmful low-threshold mechanical stimuli [1,2]. The objective of our study was to characterize differential sensitivity changes of C-fibre related subclasses of high-threshold and low-threshold polymodal nociceptors and low-threshold mechanoreceptors to the local anaesthetic (LA) mepivacaine during nerve block of the purely sensory lateral femoral cutaneous nerve (LFCN) in human. We assumed a diverse response of different classes of afferents to the two different concentrations of the LA mepivacaine (Scandicaine).

Methods: In a double-blind randomized experimental setting, an ultrasound-guided nerve block of the LFCN was performed in 10 healthy male subjects, each with two different concentrations of mepivacaine (0.5 and 1%). Responsiveness of afferent nerve fibres to different noxious and non-noxious stimuli was tested by Quantitative Sensory Testing (QST) 30, 180, and 300 min after nerve block. Both LA concentrations of mepivacaine were compared for time course of the areas of anaesthesia for the tested sensory modalities.

Results: Initial extension of anaesthetic areas at 30 min did not differ between both LA concentrations. At 180 min only the anaesthetic areas to nociceptive stimuli were reduced at the site of lower mepivacaine injection (260 mN: 204 mm^2 (18; 244; median difference and 95% confidence interval; $p < 0.05$), heat: 276 mm^2 (3; 305)). In contrast, no significant differences were found between the two concentration when non-nociceptive stimuli were used (100 mN: 187 mm^2 (4; 240), $p > 0.05$, brush: 159 mm^2 (−59; 202)).

Conclusion: Equal initial sizes of anaesthesia areas for all sensory modalities can be explained by supramaximal perineural LA molecule concentration in both administered mepivacaine dosages. Upon washout of the LA nociceptive function is restored faster as compared to non-nociceptive sensation and higher concentration of the LA are required to maintain the analgesia. Quantitative sensory testing is able to detect different susceptibility of low threshold mechanosensors and subtypes of nociceptive C-fibres to mepivacaine. Using painful mechanical, heat and electrical stimulation different classes of nociceptors will be activated. The analgesic areas to electrical stimulation were particularly small; one might therefore hypothesize that the proposed protocol allows to also differentiate mechano-insensitive ("silent") and mechanosensitive ("polymodal") nociceptors.

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Implications: QST is a non-invasive method to functionally examine sensory modalities and their pharmacological modulation in humans. The method is sufficiently sensitive to differentiate the analgesic properties of mepivacaine at 0.5 and 1% and might also be adequate to different classes of nociceptors. Further development of nociceptive stimuli including supra-threshold encoding characteristics will enable to investigate peripheral analgesic effects more specifically and thus might help to design new analgesics with preferential effect on high frequency discharge of nociceptors.

1. Introduction

Peripheral nerve blocks are frequently used in the diagnosis and therapy of acute and chronic pain. There are well accepted recommendations of local anaesthetic (LA) concentrations for use in peripheral nerve blocks in pain medicine literature. In previous studies, as described long ago [3,4], sensory and motor nerves reveal certain susceptibilities to mechanical lesions or pressure, but also to drugs like cocaine, according to their different anatomical characteristics. Nowadays somatosensory analyses can be performed by standardized techniques of quantitative sensory testing (QST), which have been established recently for patients with neuropathic pain [5,6]. Furthermore, microneurography permitted further functional differentiation of different C-fibre classes (polymodal nociceptors vs. mechano-insensitive "silent" nociceptors and sympathetic efferents) in human skin. It is of particular importance, that nociceptor classes defined by their sensory sensitivity reveal characteristic differences of their axonal conduction characteristics [7–9] suggesting differential axonal expression of ion channels and pumps involved in action potential generation; among other mechanisms slow inactivation of the voltage dependent sodium channel $Na_v1.8$ has been suggested to underlie the key differing feature, i.e. activity dependent slowing of conduction velocity [10].

A complete functional characterization of different nociceptive modalities during nerve block being used frequently in diagnostics of neuropathy has not been described before. However, it is essential to know the functional pattern of a nerve block and its concentration dependency, in order to develop future pain management strategies for chronic pain patients [11–13].

The objective of this study was to identify temporal and dose-dependent sensory characteristics of a mepivacaine-induced block of low thresholds mechano-sensitive afferents and nociceptor subclasses by using QST examination techniques [8]. For functional testing, the lateral femoral cutaneous nerve (LFCN) innervating the upper and outer thigh was selected for blockade as it is a purely sensory nerve, it is easily accessible, and it has a large innervation territory. We hypothesized that nociceptors would have a higher susceptibility to mepivacaine based on its preferential block of nociceptor-specific sodium channel Nav 1.8 [10,14]. Specific analgesic and anaesthetic characteristics for different C-fibre subtypes, such as duration of hypoesthesia and hypoalgesia and differences in size of anaesthesia areas, should be observed.

2. Methods

The study had been approved by the Institutional Review Board ("Mannheim Medical Faculty Ethics Committee") conform to international ethical standards. All participants provided written informed consent in accordance with the Declaration of Helsinki prior to participation. Participants were scanned for health risks to exclude any central or peripheral neurological deficits. Ten healthy Caucasian male subjects of similar age, height, and weight participated in this experimental study. The mean (SEM) age of the participants was 30.9 ± 6.3 years (range 22–36 years). Height and weight expressed as mean ± standard error of the mean (SEM) were 180.6 ± 1.9 cm and 74.6 ± 8.4 kg, respectively.

2.1. Study design

This study was designed as a double-blind randomized study. Syringes with LA, containing 1% or 0.5% mepivacaine, were prepared and blinded by a study nurse. Mepivacaine (Scandicaine, AstraZeneca, UK) was chosen because of its fast onset and short-acting properties. Mepivacaine 1% is a commonly used concentration in clinical practice. In our study, we divided this concentration by half (0.5%) to provoke distinctive changes of conduction properties in nociceptors detectable by QST techniques. The study nurse kept track that each subject received a nerve block of the LFCN with the higher LA concentration ($n = 10$) in one leg in one session and the lower LA concentration ($n = 10$) in the opposite leg in another session. Order of the application of the two LA concentrations was randomized. The physician conducting the nerve block, the subjects themselves, and the examiner were blinded to the two different concentrations. All blocks were applied by the same investigator who had substantial expertise in this regional anaesthesia technique.

2.2. Ultrasound-guided nerve block of the lateral femoral cutaneous nerve (LFCN)

This study was conducted with a commonly used ultrasound device (Acuson X150, Siemens, Germany) helping to identify the anatomical structures surrounding the LFCN and, thereby, allow exact positioning of the needle near the nerve [15].

By using an 11.4 MHz linear ultrasound probe approximately 1 cm distal to the anterior superior iliac spine, the sartorius muscle was identified as a triangular shaped muscle, serving as a guidance structure for the LFCN. A G27-needle was inserted parallel (out-of-plane) to the ultrasound probe in between the two sartorius fasciae by which the lateral femoral cutaneous nerve is enwrapped. The location of the needle could be visualized and followed on the screen of the ultrasound device.

A total volume of 3 ml mepivacaine was injected into the area of interest. The injection volume was continuously visualized by ultrasound as it spread between the fascia sheets of the sartorius muscle anatomically surrounding the LFCN. On the ultrasound screen, a lenticular shaped black cavity representing the injected fluid could be recognized upon LA injection, pushing the upper and lower fascia sheet apart.

After successful installation of the peripheral nerve block, the subjects were prepared for QST.

2.3. QST and sensory mapping

Standard tools for QST were utilized to measure the mepivacaine-induced sensory deficits after nerve block including pinprick, brush, painful electrical and painful heat stimuli [5,16,17]. Anaesthetic areas were assessed for the different stimuli during three time intervals: 30, 180, and 300 min after the injection of the LA. The borders of the anaesthetized areas were marked using different colours for the sensory qualities and diverse symbols for the three time intervals, conforming to the method of "sensory mapping" [17] (specimen in Fig. 1). The following colour coding was used: 100 mN pinprick = black, 260 mN pinprick = red,

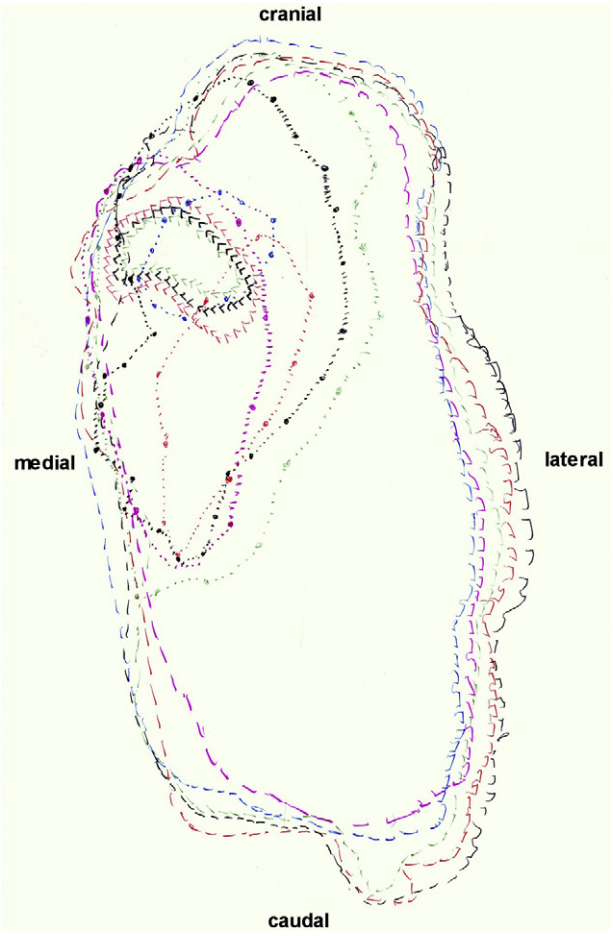

Fig. 1. Colour coding was used to differentiate sensory nerve fibre qualities (100 mN pinprick: black, 260 mN pinprick: red, brush: green, electric stimulation: blue, heat: purple) and symbols represent time points (dashes = 30 min, circles = 180 min, triangles = 300 min after nerve block application). The obtained sensory maps were copied to a transparent sheet and scanned in by a computer scanner. Anaesthetic areas for each sensory quality and time point were measured off-line by a DICOM computer program (OsiriX, Apple) and transferred to a chart where they could be statistically analyzed.

brush = green, electric stimulation = blue, heat = purple. Additionally, symbols helped differentiate between different time intervals: dashes = 30 min, circles = 180 min, triangles = 300 min after nerve block application (see Fig. 1).

In preparation for this study, several trial sessions of methodology had taken place in the original setting of the study during which the examiner became entrusted with the QST equipment under supervision of QST-experienced medical staff. According to the recommendations of the German Research Network on Neuropathic Pain (DFNS), subject's eyes were closed throughout measurements, while the examiner used exactly the same wording for instructions and the same manner of conducting the tests in all subjects [6]. The examiner performing the sensory mapping was blinded to the concentration used for the nerve block.

2.3.1. Pin prick stimulation

Von Frey's hairs (Touch Test Sensory Evaluator, North Coast Medical, Morgan Hill, USA) were used for punctate mechanical stimulation. First, a 260 mN stimulus was applied to the unaffected skin, peripherally of the anaesthetized area of the LFCN, where subjects reported a clear needle-like pin-prick sensation. This enabled subjects to compare stimulus perception with and without anaesthesia. The participant was then instructed to report each pin-prick sensation during testing. The 260 mN pin-prick stimuli were applied at about 1 Hz and moved in steps of 0.5 cm from the unaffected skin region towards the centre of the anaesthetized area. The test site at which the subject registered a change of pin-prick sensation was marked with a marking pen. This procedure was repeated until a circular skin area evolved mapping the area anaesthetic to the test stimulus. The sensory mapping procedure was repeated in exactly the same manner during a second testing session with a non-pricking 100 mN nylon filament which produced an intense static touch sensation. C-fibre afferents start responding to subjectively non-painful mechanical stimuli of 50 mN and higher [8]. By using two different intensities of pin-prick high-threshold and low-threshold polymodal nociceptors should be tested.

2.3.2. Dynamic touch stimulation

As recommended in QST protocols [17], brushing stimuli were applied centrifugally by a calibrated soft brush (Somedic, Sweden) with test strokes given at about 1 Hz and in steps of 0.5 cm from the centre towards the outskirt of the anaesthetized area. The spots at which strokes were first perceived were marked. This stimulus is a test for rapidly adapting low threshold A-fibres, albeit also C-tactile afferents were activated [18].

2.3.3. Electrically induced pain

A pointed electrode (9 mm diameter) was connected to a constant current stimulator (DS7A Digitimer Ltd., Welwyn Garden City, UK) triggered by a pulse generator (Rimkus Medizintechnik, Parsdorf, Germany). Electrical stimulation was applied with constant current pulses (5 mA, 0.5 ms, 1 Hz) from centre to periphery and provoked a sharp superficial stinging pain in normal skin. As described above, the skin area first perceiving electrically evoked stinging pain by high-threshold nociceptors was mapped and marked on the skin.

2.3.4. Heat pain

In the anaesthetized area of the LFCN, the responsiveness to a heat stimulus was examined. A surface thermode (MSA Thermal Stimulator, 9 mm × 9 mm, Somedic, Sweden) was heated to 45 °C, beyond the thermo-neutral range (31–36 °C) [19]. In steps of 2 cm, the thermode was moved from the non-anaesthetized area at the edge of the LFCN-supplied thigh area towards the numb area. The skin area insensitive to heat-evoked pain mediated by heat-sensitive polymodal nociceptors was mapped and marked.

2.4. Off-line measurements of the anaesthetized areas

All sensory nerve fibre qualities of the LFCN were tested for function in each subject 30, 180, and 300 min after the injection of mepivacaine. Colours were used to differentiate the tested sensory nerve qualities (100 mN and 260 mN pin-pricks, brush, electrical pain and heat pain).

The assessment of each time interval (30, 180, 300 min) took approximately 30 min. Mapping of pin-prick sensitivity and for electrical stimuli was straight forward and took about five minutes; differentiation of temperature and brush strokes was more difficult for the subjects and thus mapping took about 10 min. The order of sensory stimuli in the QST protocol was kept identical between the sessions. The completion of all three testing sessions took approximately 6.5 h for each individual altogether. Finally, after all three sessions had been completed, the marks on the thigh of the subject resulted in a "sensory map" which was copied by hand to a transparent sheet and then scanned in with a computer scanner at 300 dpi. Additionally, a digital photo was taken for documentation. Anaesthetic areas for each sensory quality and time point were measured off-line by a DICOM computer program (OsiriX, Apple) and their values were listed in a chart.

2.5. Data evaluation

All data were analyzed using adequate statistical software (Statistica 6.0, StatSoft, Tulsa, USA). Significant effects on the size of the anaesthetic area were calculated by repetitive measures analysis of variance (ANOVA) with the grouping variables "LA concentration", "sensory test" and "time of assessment". To identify significant differences of the time course of the LFCN blockade, Wilcoxon's matched pairs tests were used as post hoc tests to analyze differences in the areas of the anaesthetic zones in the time intervals 30 – 180 – 300 min ("time of assessment" Also, Wilcoxon's matched pairs tests were used to identify significant effects of the employed sensory tests ("100 mN" – "260 mN" – "brush" – "heat" – "electrical pain") on the anaesthetic areas in the time intervals 30 – 180 – 300 min. Significance levels were set at $p \leq 0.05$ and data are depicted as medians (25 and 75 percentiles) with 95% confidence intervals.

3. Results

We aimed to identify nociceptive differences in the time course of the nerve fibre block and in dependence of the two concentrations of administered local anaesthetic (LA). Data of twenty LFCN blocks, half of them with 1.0% and the other half with 0.5% mepivacaine, were assessed and analyzed for different QST results (see Fig. 2).

Temporal axonal characteristics were tested by assessing the area of anaesthesia at three time intervals (30, 180, and 300 min after nerve block). We analyzed whether a concentration change of LA altered the course of time. ANOVA analyses revealed a time-dependency of peak anaesthetic areas for all fibre functions ($p < 0.0005$). Maximal spreads of anaesthetic areas were recorded at 30 minutes after nerve block initiation, followed by considerable decreases of anaesthetic area sizes at 180 minutes (see Fig. 2). At 300 min after nerve block initiation only 30% of subjects with 0.5% and 30% of volunteers with 1.0% mepivacaine had measurable areas for mechano-sensitive polymodal C-fibres (pin-prick, brush), and about 10% of subjects showed measurable areas for heat and electrical stimuli (not shown in Fig. 2).

The effect of LA concentration change on different nociceptive modalities was tested and indicated a significant impact ($p = 0.044$, ANOVA). Even though at 30 min no significant differences of the registered anaesthetic areas were analyzed between concentrations and modalities ($p \geq 0.616$, ANOVA), dose-dependent differences were found between nociceptive and non-nociceptive stimuli after 180 min. In particular, nociceptive fibres responsive to high-threshold pain stimuli (260 mN and heat) proved to be more sensitive to dosage changes of LA ($p = 0.028$, median difference (π) between concentrations with 95% CI 204.25 (18.16; 244.23) (260 mN), and $p = 0.028$, $\mu = 276.04$ (3.59; 305.64) (heat), Wilcoxon's matched pairs test, see Fig. 2A and B with 95% confidence intervals (CI)). The mean values of electrical pain stimulation showed no significant differences (see Fig. 2C) ($p = 0.093$, $\pi = 152.23$ (−50.09; 312.68) (5 mA), Wilcoxon's matched pairs test) and showed the highest distribution of values (range 0; 714.11 cm^2). Somatosensation to low-threshold stimuli (100 mN and brush) showed no significant changes of anaesthetic areas in response to the LA dosages ($p = 0.051$, $\pi = 186.97$ (4.33; 240.08) (100 mN) and $p = 0.086$, $\mu = 159.17$ (−59.69; 202.31) (brush), Wilcoxon's matched pairs test) (see Fig. 2, D+E, including 95% CI). Noteworthy, heat sensitive nociceptors showed a pronounced change of area size in time dependant on LA concentration when compared to the other nociceptive qualities (p[time × concentration (heat)] = 0.039, ANOVA) (see Fig. 2C). The observed impact of the LA blockade on the sensory modalities, e.g. C-fibre-mediated nociception and touch (Fig. 2)

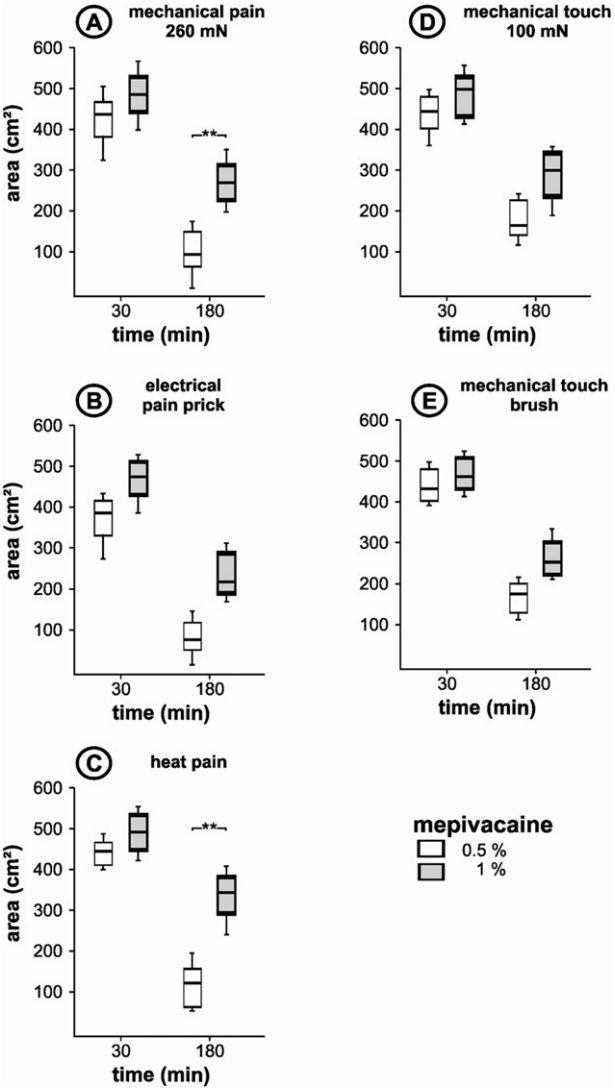

Fig. 2. Dose-dependent functional changes of the anaesthetic areas after injection of mepivacaine (0.5% vs. 1%) performed with QST. High-threshold nociception conduction nerve fibres show significantly smaller anaesthetic areas established with lower mepivacaine dose (A and C), whereas in low-threshold axons (D and E) and electrical stimulation (B) dose alterations did not reveal significant size changes in anaesthetic areas ($p < 0.05$, ANOVA). Boxplots present medians and 25 and 75 percentiles; limits refer to 95 confidence intervals.

may encourage future research to further differentially explore the clinical behaviour of particular subsets of sensory skin afferents to help define pharmacological profiles of analgesia.

4. Discussion

In our study blockade of the LFCN was successfully used to assess functional sensitivity changes of different subclasses of nociceptive C-fibres during anaesthesia with mepivacaine in humans. By using two different dosages of mepivacaine – a frequently used and well-known sodium channel blocker – we could show different sensitivity of high-threshold (heat and 260 mN pin-prick) vs. low-threshold nociceptive nerve fibres (100 mN pin-prick, brush) [11–13].

In this study, sensory testing of receptive endings in the skin was linked to axonal application of local anaesthetics which might appear inappropriate at first glance. However, there is a surprisingly tight link between axonal characteristics of primary afferent fibres and their sensory function: activity dependent slowing of

conduction can be used to differentiate polymodal nociceptors, silent nociceptors, cold nociceptors and sympathetic efferent fibres [7–9]. Thus, we hypothesized that based on the axonal conduction differences also responsiveness to local anaesthetics might differ between fibre classes.

The results demonstrate that both concentrations of mepivacaine result in a comparably large initial anaesthetic area. Therefore, both concentrations were initially high enough to completely block conduction (supramaximal dosage), and resulted in comparably maximal anaesthetic areas. A faster decline of high-threshold nociceptive responses for the (low) 0.5% concentration of mepivacaine can be explained by pharmacokinetic features with a half-life of mepivacaine of about 1.9–3.2 h [20]. Selectively examining mechano-sensitive and mechano-insensitive nociceptors, the two concentrations did not differ significantly in their anaesthetic effects despite the assumed differences in axonal sodium channel expression in these nerve fibres [7]. However, a more sensitive response to concentration alteration could be seen in high-threshold nociceptors vs. low-threshold nociceptors, which indeed could be due to different axonal sodium channel expression. A non-significant wide-ranged response of nociceptors reacting to electrical stimuli could be explained by insufficient strength of the stimulus regarding the nociceptive activation threshold of high-threshold mechano-insensitive nociceptors in several subjects [8].

Different sub-types of sodium channels have been characterized in the somata of thin afferent axons with respect to their sensitivity against the buffer fish venom tetrodotoxin (TTX), being either TTX-sensitive or TTX-resistant. Expression of TTX-resistant sodium channels is generally higher in nociceptors, and thus, a lower sensitivity of TTX-resistant sodium channels to mepivacaine could explain our results [21–24]. Among the subtypes of voltage-gated sodium channels, $Na_v1.7$, $Na_v1.8$ and $Na_v1.9$ play crucial roles in nociception and chronic pain. However, IC 50 values for static and use-dependent block by mepivacaine did not differ considerably between TTX-resistant and other voltage-dependent sodium channels [25,26]. Yet, recent results suggest a preferential block of nociceptor-specific $Na_v1.8$ by mepivacaine [14] which would predict a higher susceptibility of certain nociceptor-subtypes carrying a larger number of this channel to mepivacaine.

A distinct distribution of voltage-gated sodium channels with a lower density in nociceptive C-fibre afferents might be another explanation for the observed differences in mepivacaine sensitivity. Upon injection, a high concentration of the LA will reach the membrane and bind to sodium channels. The non-bound fraction will be prone to wash-out, whereas the bound fraction will provide a reservoir of LA. This reservoir will be similar for the two concentrations as both are supposed to be supra-maximal. The faster decline of tissue concentrations for the 0.5% mepivacaine might be more relevant for conduction of C-fibres that possess a lower number of sodium channels (or a different expression pattern) being bound by LA-molecules in the preliminary LA flooding. The correlation between morphology of dendritic arborisations in diverse C-nociceptors and their distinct expression in number and type of voltage-gated ion channels are subject of on-lasting intense research [27]. Low-threshold A-fibres might also contribute to the perception of low-threshold nociceptive stimuli where a reservoir of the LA can be built up at the nodes of Ranvier and explain the less pronounced concentration dependency for the myelinated fibres.

We found functional differences between nociceptors and low-threshold mechanosensitive fibres by using QST techniques in a reversible sodium channel block of the LFCN. There was a similar onset of the block in the different fibre types, yet the reversal was faster in the nociceptors. In particular, polymodal nociceptors tested by heat stimuli were more sensitive to concentration changes of the LA.

We did a proof-of-principle study demonstrating pharmacological differences between two concentrations (0.5% and 1%) of the commonly used LA mepivacaine using quantitative sensory testing. Understanding the effect of local anaesthetics on particular sub-classes of primary afferent nociceptive neurons including new neurophysiological targets could help define pharmacological profiles of analgesics and, thus, improve efficacy of its use in pain therapy in the future. Several mechanisms of action have to be taken into consideration explaining the different profile of C-fibre afferents including sodium channel subtype physiology and distribution. Fibre type-specific axonal expression of sodium channels might provide selective targets for new analgesics that preferentially block nociceptive responses. The combination of non-invasive method of QST, axonal application of compounds and fibre type specific sensory stimuli can be an effective and easy-to-use test method in humans.

Author contributions

C. Menzer and M. Schley: designed the study, conducted the study, analyzed the data and wrote the manuscript.

Roman Rukwied and Martin Schmelz: designed the study, analyzed the data and wrote the manuscript.

Martin Dusch: design the study.

Justus Benrath: designed the study, conducted the study, analyzed the data, wrote the manuscript and performed the ultrasound-guided nerve blocks.

Conflict of interest

None.

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References

[1] Bjornsdotter M, Morrison I, Olausson H. Feeling good: on the role of C fiber mediated touch in interoception. Exp Brain Res 2010;207:149–55.
[2] Schmelz M, Schmidt R. Microneurographic single-unit recordings to assess receptive properties of afferent human C-fibers. Neurosci Lett 2010;470:158–61.
[3] Luederitz. Versuche über die Einwirkung des Druckes auf die motorischen und sensiblen Nerven. Z Klin Med 1881;Band II.
[4] Gasser H, Erlanger J. The role of fiber size in the establishment of a nerve block by pressure or cocaine. Am J Physiol 1929;88:581–91.
[5] Arendt-Nielsen L, Yarnitsky D. Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. J Pain 2009;10:556–72.
[6] Rolke R, Baron R, Maier C, Tolle TR, Treede RD, Beyer A, Binder A, Birbaumer N, Birklein F, Botefur IC, Braune S, Flor H, Huge V, Klug R, Landwehrmeyer GB, Magerl W, Maihofner C, Rolko C, Schaub C, Scherens A, Sprenger T, Valet M, Wasserka B. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. Pain 2006;123:231–43.
[7] Obreja O, Ringkamp M, Namer B, Forsch E, Klusch A, Rukwied R, Petersen M, Schmelz M. Patterns of activity-dependent conduction velocity changes differentiate classes of unmyelinated mechano-insensitive afferents including cold nociceptors, in pig and in human. Pain 2010;148:59–69.
[8] Weidner C, Schmelz M, Schmidt R, Hansson B, Handwerker HO, Torebjork HE. Functional attributes discriminating mechano-insensitive and mechano-responsive C nociceptors in human skin. J Neurosci 1999;19:10184–90.
[9] Campero M, Serra J, Bostock H, Ochoa JL. Partial reversal of conduction slowing during repetitive stimulation of single sympathetic efferents in human skin. Acta Physiol Scand 2004;182:305–11.

[10] De Col R, Messlinger K, Carr RW. Conduction velocity is regulated by sodium channel inactivation in unmyelinated axons innervating the rat cranial meninges. J Physiol (Lond) 2008;586:1089–103.
[11] Mackenzie RA, Burke D, Skuse NF, Lethlean AK. Fibre function and perception during cutaneous nerve block. J Neurol Neurosurg Psychiatry 1975;38:865–73.
[12] McGlone F, Vallbo AB, Olausson H, Loken L, Wessberg J. Discriminative touch and emotional touch. Can J Exp Psychol 2007;61:173–83.
[13] Schlereth T, Magerl W, Treede R. Spatial discrimination thresholds for pain and touch in human hairy skin. Pain 2001;92:187–94.
[14] Leffler A, Reckzeh J, Nau C. Block of sensory neuronal Na+ channels by the secreolytic ambroxol is associated with an interaction with local anesthetic binding sites. Eur J Pharmacol 2010;630:19–28.
[15] Gadsden J, McCally C, Hadzic A. Monitoring during peripheral nerve blockade. Cur Opin Anaesthesiol 2010.
[16] Backonja MM, Walk D, Edwards RR, Sehgal N, Moeller-Bertram T, Wasan A, Irving G, Argoff C, Wallace M. Quantitative sensory testing in measurement of neuropathic pain phenomena and other sensory abnormalities. Clin J Pain 2009;25:641–7.
[17] Walk D, Sehgal N, Moeller-Bertram T, Edwards RR, Wasan A, Wallace M, Irving G, Argoff C, Backonja MM. Quantitative sensory testing and mapping: a review of nonautomated quantitative methods for examination of the patient with neuropathic pain. Clin J Pain 2009;25:632–40.
[18] Wessberg J, Olausson H, Fernstrom KW, Vallbo AB. Receptive field properties of unmyelinated tactile afferents in the human skin. J Neurophysiol 2003;89:1567–75.
[19] Yarnitsky D, Ochoa JL. Studies of heat pain sensation in man: perception thresholds, rate of stimulus rise and reaction time. Pain 1990;40: 85–91.
[20] Wishart DS, Knox C, Guo AC, Cheng D, Shrivastava S, Tzur D, Gautam B, Hassanali M. DrugBank: a knowledgebase for drugs, drug actions and drug targets. Nucleic Acids Res 2008;36(Database issue):D901–6.
[21] Lang PM, Hilmer VB, Grafe P. Differential contribution of sodium channel subtypes to action potential generation in unmyelinated human C-type nerve fibers. Anesthesiology 2007;107:495–501.
[22] Fjell J, Hjelmstrom P, Hormuzdiar W, Milenkovic M, Aglieco F, Tyrrell L, Dib-Hajj S, Waxman SG, Black JA. Localization of the tetrodotoxin-resistant sodium channel NaN in nociceptors. Neuroreport 2000;11:199–202.
[23] England S. Voltage-gated sodium channels: the search for subtype-selective analgesics. Expert Opin Investig Drugs 2008;17:1849–64.
[24] Momin A, Wood JN. Sensory neuron voltage-gated sodium channels as analgesic drug targets. Curr Opin Neurobiol 2008;18:383–8.
[25] Brau ME, Branitzki P, Olschewski A, Vogel W, Hempelmann G. Block of neuronal tetrodotoxin-resistant Na+ currents by stereoisomers of piperidine local anesthetics. Anesth Analg 2000;91:1499–505.
[26] Brau ME, Elliott JR. Local anaesthetic effects on tetrodotoxin-resistant Na+ currents in rat dorsal root ganglion neurones. Eur J Anaesthesiol 1998;15: 80–8.
[27] Hall DH, Treinin M. How does morphology relate to function in sensory arbors? Trends Neurosci 2011;34:443–51.