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Editorial comment

A novel approach of analyzing characteristics of sensory nerve fibers

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In this issue of the *Scandinavian Journal of Pain*, Menzer et al. [1] report on the spatial components of a nerve branch block induced by two different doses of mepivacaine, a short acting local anesthetic. Apart from an obvious difference on duration of the block by two different concentrations administered, 5 mg/ml and 10 mg/ml, and in the spatial extension of the block, there were also some differences between different sensory modalities.

In spite of the long time that local anesthetics have been available, there are very few studies describing the differential effects of local anesthetics, i.e. unselective sodium channel blockers, on specific, different sensory modalities. This is true for temporal and spatial components. Previous studies have focused mainly on graded levels of motor block and on dicotomous yes/no assessments of "surgical anesthesia".

1. Neuropathic pain and sodium channels NaV1.7, NaV1.8, and NaV1.9

In light of the high interest during the latter years in the role of the different sodium channels, both NaV1.7, recently also NaV1.8, and possibly even NaV1.9, in neuropathic pain, this type of knowledge is of great importance. This is not only for the understanding of neuropathic pain per se, but also as a tool for the development of new treatments for neuropathic pain. Basic knowledge in healthy volunteers helps our understanding and interpretation of patient studies.

It has been suggested that especially the NaV1.7 channel is of key importance in ongoing neuropathic pain, as exemplified by e.g. Dib-Hajj et al. [2], linking gain-of-function mutations in the NaV1.7 channel to erythromelalgia. However, recent genetics data presented at the IASP-World Congress in Milan 2012 [3] suggest that the NaV1.7 mutations causing the painful erythromelalgia are not the only important ion channel mutations causing chronic neuropathic pain. It is therefore crucial to have an accurate and reliable assessment method of normal nerve function, that does not depend on super-specialty skilled staff and equipment like microneurography to obtain reliable clinical data.

It is now necessary to correlate labor intense microneurographic studies with the presently described methodology [1] in order to link the peripheral specific nociceptor function to more proximal axon functional data, as well as the effects of a robust positive control marker for differential sodium channel blockade. In vitro studies of sodium channel functionality can contribute important knowledge on the basic science, but a clinical functional correlate is essential for relevant interpretation of the experimental data. In that respect, the current study by Menzer et al. [1] can contribute with an important step in the translational chain of knowledge from animal and human in vitro data to healthy humans to patient.

2. The approach by Menzer et al. [1] is novel

Their method addresses the nerve transduction properties of afferent sensory fibers. Data published on peripheral nerve block by, e.g. compression block, only differentiates A-beta and A-delta myelinated fibers from non-myelinated C fibers. Others, like Quiding et al. [4] and Weinkauf et al. [5] describe studies where healthy volunteers have been subjected to a quantitative sensory approach by local intradermal injection of lidocaine in intact skin and nerve growth factor (NGF) treated skin. Both studies demonstrated a dose–response relationship at doses below and similar to Menzer et al. [1]. They have demonstrated that sensitivity both to heat and to mechanical pain stimulation was significantly altered by 0.1 mg/ml and 1 mg/ml of lidocaine. Mechanical pain sensitivity was more sensitive to lidocaine in lower concentrations. However, in those studies, the area of block was not studied, due to the local character of the administration of the local anesthetic. However, cold detection thresholds (CDTs) were not affected by the local anesthetic [4,5].

3. Different effects of local anesthetic on heat pain, pin-prick pain, brush stimulation

The block was maintained longer for heat pain for the high concentration, but also for mechanical pain on 260 mN pin prick, but not for brush stimulation or for light mechanical touch stimulation by 100 mN. The differences were discrete but still statistically significant, and in line with findings from other studies [4–7].

The temporal and dose-dependent sensory characteristics of a local anesthetic block on low-threshold mechano-sensitive afferents and nociceptors, as well as nociceptor sub-classes are of importance for mechanistic understanding of neuropathic pain. A-delta fiber function, measured by cold detection threshold (CDT),

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clearly showed a dose–response relationship. However, C-fiber functions varied.

Methodological challenges may be present due to the administration mode of local anesthetic to the lateral cutaneous femoral nerve. The authors are clear on the mechanism of duration of block, based on volume, concentration and the effect site on the inside of the neural membrane. However, there are no clear-cut differences between modalities, but rather graded differences, some of which are of the effect size to provide a statistically significant difference. This is due to differences in fiber properties, but it may also be due to a reflection of different localization of modalities of C-fibers within the nerve trunk. Therefore, a factor of diffusion may play a role. Thus, correlating the results of the present study by Melzer et al. to microneurography data from the same group is of importance in order to validate the findings. The authors have described the reasons for choosing the lateral cutaneous femoral nerve in order to reduce confounding factors.

Results are also in line with the long-standing notion that the thicker the fiber the higher concentration needed for a conduction block [7]. However, the responses may be different after nerve injury. This would need a separate study in a stratified patient cohort: do axones of sensitized nociceptors (since this is the available phenotype that can be readily assessed) respond similarly to local anesthetic direct nociceptor block and nerve conduction block [6]?

However, recent studies of transdermal lidocaine patches are not comparable to studies of lidocaine injection in other respects, e.g. that the concentration at effect site is unknown and that the time factor of skin penetration is not clear, except for the lidocaine-prilocaine mixture EMLA [8]. This implies that the tissue penetration to effect site differs and depends on the distance to the peripheral nociceptor in question. The present study by Menzer et al. [1] overcomes several of these methodological confounders as mepivacaine was injected directly adjacent to the nerve axon.

4. Minimally invasive measurements of different peripheral nociceptors [1]

Refining the presently used technique further may make it possible to differentiate between different peripheral nociceptors and thus types of C-fibers by using a minimally invasive measurement. Fiber and modality discriminations were described using single C-fiber recordings with microneurography. This method requires special equipment and extensive training. This group of researchers, one of the few who are experienced in microneurography, now must correlate electrophysiology to psychophysics and functionally investigate the pharmacodynamics of NaV-blockers in different fiber types. Translating mechanisms between the two different technical methodologies provides strengths to both techniques.

A tool that is more easily applied than microneurography and that would give robust information, could then be used more widely as a tool in investigating e.g. the potential effect of more selective NaV channel blockers.

5. Important implications for evaluating new analgesic drugs

Demonstrating differences between C-fibers could be of importance for NaV-channels and for other types of ion channels where local anesthetics may excert their action, e.g. the transient-receptor-potential-vaniloid (TRPV) channels. From a mechanistic perspective, a comparison of the gradual effects of lidocaine on warmth, the more dichotomous response to heat could be related to differences in receptors, nerve impulse propagation and/or conduction. The receptors are however of the same family, probably TRPV1 for heat pain and TRPV3 and possibly TRPV4 for warmth, and the differences may therefore be related to potential differences in sensitivity and distribution of sodium channels. The results may indicate different nerve impulse propagation/transmission for warmth and heat sensation e.g. different proportions of sodium channel isomers related to warmth and heat sensation.

Thus, the described model for pharmacological investigations of nerve conduction could be an auxiliary tool to peripheral drug administration and electrophysiology in studying effects of new analgesic compounds with peripheral mode of action affecting action potentials.

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