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Primary afferent input critical for maintaining spontaneous pain in peripheral neuropathy

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ABSTRACT

Central sensitization after peripheral nerve injury may result in ectopic neuronal activity in the spinal cord dorsal horn, implying a potential autonomous pain-generating mechanism. This study used peripheral nerve blockade and systemic lidocaine administration, with detailed somatosensory assessment, to determine the contribution of primary afferent input in maintaining peripheral neuropathic pain. Fourteen patients with neuropathic pain (7 with unilateral foot pain due to peripheral nerve injury and 7 with bilateral pain in the feet due to distal polyneuropathy) underwent comprehensive characterization of somatosensory function by quantitative sensory testing. Patients were then administered an ultrasound-guided peripheral nerve block with lidocaine and intravenous lidocaine infusion in randomized order. The effect of these interventions on spontaneous pain intensity and on evoked cold, warm, pinprick, and brush responses was assessed at each session. All patients had sensory disturbances at baseline. The peripheral nerve block resulted in a complete abolition of ipsilateral pain within 10 min (median) in all patients, with lidocaine plasma concentrations being too low to account for a systemic effect of the drug. Intravenous lidocaine infusion reduced the spontaneous pain by 45.5% (±31.7%), and it reduced mechanical and thermal hypersensitivity in most patients who displayed such signs. However, the improvement in evoked hypersensitivity was not related to the effect of the drug on spontaneous pain intensity. This study demonstrated that regardless of the individual somatosensory phenotype and signs of central sensitization, primary afferent input is critical for maintaining neuropathic pain in peripheral nerve injury and distal polyneuropathy.

1. Introduction

Neuropathic pain, which is caused by a lesion or disease affecting the somatosensory system [18], is a disabling condition affecting up to 7% to 8% of the general adult population [6,35]. It is characterized by the presence of spontaneous ongoing and evoked pain, with the latter presenting as allodynia (pain elicited by a non-noxious stimulus) or hyperalgesia (increased pain response to a noxious stimulus) [9,10]. There is now abundant experimental and clinical evidence to indicate that both peripheral and central changes contribute to the neuronal hyperexcitability that is characteristic of neuropathic pain [29,40,43].

In nerve injury and peripheral neuropathies, release of trophic factors [3,13], increased activity of transient receptor potential vanilloid channels [16,20], dysregulation of voltage-gated ion channels [1,4,40], and sprouting of peripheral nerve endings [12] are some of the changes contributing to peripheral hyperexcitability. This hyperexcitability also affects dorsal root ganglion cells and subsequently the spinal cord dorsal horn, where alterations of sodium channel expression, microglia hyperactivation, and dendritic sprouting are among the typical changes after peripheral nerve damage [24,32,38]. This plasticity occurring within the dorsal horn, coupled with impaired descending pain modulation [42], is known as central sensitization [41,43]. The clinical

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translation of these changes in the peripheral and central nervous systems is not straightforward; it is assumed to include enhanced responses to noxious stimuli, pain produced by innocuous thermal and mechanical stimuli, a spread of pain and sensory abnormalities outside the damaged nerve territory, and enhanced temporal summation [9,17,40].

Despite the involvement of peripheral and central mechanisms in neuropathic pain, the relative contribution of the 2 sites is still unknown. It has been suggested that central sensitization after peripheral nerve damage may give rise to ectopic activity of spinal cord neurons, capable of autonomous pain generation, based on recordings from rat wide dynamic range interneurons [19,40]. Other data suggest that peripheral nerve block in rats with nerve injury can reduce the spontaneous activity of sensitized wide dynamic range neurons by about 60% [25], but the clinical translation of this phenomenon is unknown. Gracely et al. [15] described 4 cases of complex regional pain syndrome that assumed additional nerve injury, where peripheral lidocaine infiltration abolished spontaneous pain and allodynia (including outside the primary nerve injury area) for the duration of peripheral blockade. However, this study was not designed to systematically address the peripherally and centrally mediated effects of the local anesthetic or to quantitate the kinetics of relief in spontaneous pain and evoked mechanical and thermal responses. Consequently, whether spontaneous neuropathic pain requires ongoing peripheral somatosensory input or can be maintained independently by central sensitization mechanisms is still a matter of debate.

To address this question, we used peripheral nerve blocks and systemic lidocaine administration combined with pharmacokinetic assessment and detailed somatosensory examination in patients with peripheral neuropathic pain due to unilateral nerve injury or bilateral nerve damage caused by distal polyneuropathy. The primary aim was to study whether peripheral nerve blocks relieved spontaneous pain. Abolishing spontaneous pain with nerve blocks with plasma lidocaine concentrations lower than required to attain systemic response would indicate that peripheral input is critical.

2. Methods

2.1. Participants

The study was approved by the Regional Research Ethics Committee of Central Denmark (1-10-72-31-12), and individual written informed consent was obtained according to the Declaration of Helsinki [39]. Patients were recruited from the Pain Clinic and the Department of Neurology of Aarhus University Hospital, Aarhus, Denmark. Patients with chronic neuropathic pain in one foot due to a peripheral nerve injury (PNI) or bilateral pain in the feet due to distal symmetric polyneuropathy (DSP) were sent a letter inviting them to participate in the study.

Inclusion criteria were clinical neurological diagnosis of DSP confirmed by electromyography and electroneurography or skin biopsy, or PNI verified by clinical neurological examination, during surgery, or by neurophysiological examination. The patients had to have definite neuropathic pain [36], average spontaneous daily pain intensity in the last week $\geqslant 4$ (score on a 0–10 numerical rating scale, NRS); and pain that lasted 6 months or longer.

Patients were excluded in the case of age under 18 years; insufficient language or communication skills; other moderate to severe pain or any other condition treated with opioids, antidepressants, or anticonvulsants; treatment with topical local anesthetics or capsaicin in the past 3 months; other central or peripheral neurological disorder; major cognitive or psychiatric disorder; or contraindication to lidocaine or peripheral nerve block.

2.2. Experimental setting

After the screening, each patient was scheduled for 3 visits. The first visit included baseline characterization of somatosensory function, after which the patient was randomized for a peripheral nerve block vs intravenous lidocaine infusion, separated by at least 7 days. The order in which the extremities were assessed for pain and evoked responses (left, then right, or vice versa) at each time point at both treatment sessions was also randomized (Research Randomizer; http://randomizer.org). One day before the third visit, the patients were contacted by telephone to assess their pain intensity to ascertain that there would be no carryover effect of the intervention at visit 2.

2.3. Concomitant medications

Opioids, antiepileptic drugs, and duloxetine were tapered gradually and discontinued 36 h before each visit, and tricyclic antidepressants were discontinued 7 days before each visit. The patients were allowed to receive paracetamol at a stable dose, but they were required to avoid taking it 8 h before each visit.

2.4. Baseline visit

2.4.1. Questionnaires

The patients completed the following questionnaires at baseline: Hospital Anxiety and Depression Scale [45], Brief Pain Inventory [33], Neuropathic Pain Symptom Inventory [5], and PainDETECT [11].

2.4.2. Fluctuations in pain and evoked thermal and mechanical responses

Spontaneous pain (0–100 NRS, 0 = no pain, 100 = worst imaginable pain) and evoked responses to cold (20°C), warm (40°C) (Rolltemp, Somedic AB, Sweden), brush (SENSELab Brush-05, Somedic AB, Sweden), and pinprick (45 mm safety pins; Hartmann-Scandi-Care AB, Sweden) stimuli were assessed at baseline 4 times, 5 min apart and without any intervention, with the patient resting in bed. The evoked thermal and mechanical responses were evaluated on a 0–10 NRS (anchors: 0 = no sensation, 5 = normal sensation, 10 = extremely intense/painful sensation) [22], with a nonpainful area (contralateral or upper limb) as reference. This procedure was performed to minimize the possibility that "normal" fluctuations in any of these parameters during one of the treatment sessions were misinterpreted as treatment effects.

2.4.3. Quantitative sensory testing

Quantitative sensory testing (QST) was performed according to the protocol of the German Research Network on Neuropathic Pain [27,28].

Cold and warm detection thresholds, cold and heat pain thresholds, and thermal sensory limen to ascertain any paradoxical heat sensations were determined by the Thermal Sensory Analyzer (Medoc, Israel). Mechanical detection threshold was determined with a set of standardized von Frey filaments (0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, 128, and 256 mN (Nervtest, Marstock, Germany) using a modified method of limits. Mechanical pain threshold was determined with a set of 7 metal probes with standardized stimulus intensities (8, 16, 32, 64, 128, 256, and 512 mN; MRC Systems GmbHl Medizintechnische Systeme, Heidelberg, Germany) with uniform skin contact area of 0.25 mm, using a modified method of limits. Mechanical pain sensitivity of the skin and dynamic mechanical allodynia were determined by the same set of 7 metal probes with standardized stimulus intensities and in addition by a set of 7 light intensity stimuli: a cotton wool ball with a force of 3 mN, a Q-tip (fixed to a plastic stick) with a force of 100 mN,

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