Original Research Article

Sensory Small Fiber Function Differentially Assessed with Diode Laser (DL) Quantitative Sensory Testing (QST) in Painful Neuropathy (PN)

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Abstract

Sensory function of small peripheral nerve fiber was assessed by means of quantitative sensory testing (QST) during which sensory stimulation was provided using diode laser (DL) in patients suffering from painful neuropathy (PN) and compared with symptom-free healthy controls (HC). Based on previous research work using DL stimulation, parameters that demonstrated safe and specific activation of A-delta, which were distinct from stimulation parameters for the activation of C-fibers, were utilized in this study. Results of this study demonstrated that this differential activation pointed to the impaired function of A-delta fibers while C-fiber function was unaffected. Stimulation of HC reproduced previously published results, and stimulation during this study was safe also without any dermal effect in patients with PN and in HC. Parameters used in this study were demonstrated in previous preclinical rodent study identical differential effect on activation of A-delta and C-fibers, and as such, DL is an ideal tool for translational pain research where specific activation of A-delta or C-fibers, or both, is required.

Key Words. Painful Neuropathy; Diode Laser; Quantitative Sensory Testing

Introduction

Peripheral painful neuropathies (PNs) are common in clinical practice, though underdiagnosed and undertreated with debilitating results for patients. Most readily recognized examples of PNs are painful diabetic peripheral neuropathy (DPN), HIV-associated neuropathy (HAN), and chemotherapy-induced neuropathy [1]. Pain due to neuropathy remains difficult to diagnose and consequently difficult to treat, in large part due to the lack of available tools for precise assessment of the underlying small peripheral nerve fiber functional status and associated pathology. The functional status of small nerve fibers is in particular relevant to PNs because these fibers are directly involved in nociceptive processes which are the basis for the pathophysiology of neuropathic pain (NP), such as that seen in DPN or HAN. The currently available quantitative sensory testing (QST) tools, which assess small peripheral nerve function by means of thermal stimuli [2,3] provided by contact thermods, have several critical limitations and lack the ability to differentiate between specific types of small nerve fibers, A-delta vs C-fibers. A range of abnormalities in function of small myelinated (A-delta) and unmyelinated (C) fibers, ranging from deficits to hyperalgesia, is the basis of NP pathophysiology and related to the underlying NP mechanisms [4]. The ability to specifically differentiate the involvement of fiber type in NP would be an important step in NP translational research as majority of the preclinical research has been conducted based of small fiber pathophysiology [4].
Laser stimulation is used as a modality for cutaneous sensory somatic stimulation, and it activates nociceptors by heating the very circumscribed areas of top layers of skin, which is the histoanatomic location of small fiber terminal branches. Laser stimulation has a number of stimulation features, which should be considered significant advantage when compared with contact thermodes, and those include distinct stimulation onset and offset and deeper and more homogeneous heating without sensory noise from mechanical contact. However, laser stimulation based on the original CO₂ and Tm:YAG-based technologies allows only for testing of A-delta fibers as demonstrated by laser-evoked potentials (LEP)/electroencephalography recording technique. An additional shortcoming of CO₂ and Tm:YAG lasers is that the intensity of stimuli is unstable, and their variability is in the range of ±5–10% (Figure 1). They do not provide homogeneous depth of heating of the skin tissues to the depths where small fibers are located, which leads to suboptimal reproducibility of stimulation parameters, and consequently, their application for QST and for LEP are suboptimal. Diode laser (DL) was developed to improve upon the original stimulation characteristics (Figure 1), and the improvement provided by the DL technology has resulted in more specific and differential stimulation of A-delta and C-fibers [5]. This particular DL was developed for the application of painful stimuli to the human skin and has these characteristics: power of 20 W, wavelength of...

Figure 1 Temperature from kinetics simulation of skin tissue heating at different skin depths of 0, 300, and 600 microns, done with three types of lasers and their stimulation characteristics specific for each laser type: diode laser (DL)—stimulus duration 60 msec, wavelength 980 nm; Tm:YAG—5 msec, 2,100 nm; CO₂: 50 msec, 10,200 nm. The stimulation was based on assumption that baseline skin temperature at the depth of 300 μm is 36°C and that a laser would produce increase in temperature of 10°C at 300 μm depth reaching the temperature of 46°C, which is sufficient to activate transient receptor potential vanilloid 1 (TRPV1) channels and nociceptive processes that ultimately would evoke pain sensation. The surface skin temperature and the temperature at 600 μm of skin depth for each method of laser stimulation were recalculated based on the necessary laser power for each laser with pulse durations of 5 ms for Tm:YAG, 50 ms for CO₂, and 60 ms at 980 nm for DL. It should be noted that DL is the only laser type that would rapidly increase temperature by 10°C and maintain it with great stability at both skin depths of 300 μm and 600 μm.
Sensory Function Differentially Assessed with Diode Laser

980 nm, and spot diameter 1 or 5 mm (LASS-10 M, Lasmed LLC, Mountain View, CA, USA; patented in 2004). The red aiming guide light (670 nm, 5 mW) is used to point at the area of stimulation. Selective activation of A-delta-fibers was accomplished by using DL with a high-rate heating, high energy, brief pulses, and small size, 1 mm in diameter, of individual stimulation area. Selective activation of C-fibers was accomplished by low rate of tissue heating with long pulses, low energy, and larger size 5 mm in diameter of stimulation [5–10]. An important characteristic of information obtained from selective activation in human volunteers is that increase in intensity of stimulus translated in corresponding increase in pain intensity rating and in size of LEP, which were highly correlated for both, A-delta and C-fiber stimulation [8].

In this small proof of concept clinical study, the attempt was made to demonstrate differential effect of DL selective stimulation on functional status of small peripheral nerve fibers in patients with PN and compared with the results of same stimulation parameters applied to normal controls. We also discuss here the significance of information obtained from this differential stimulation.

Methods

Study subjects recruited for this study were patients with PN and healthy controls (HC), older than the age of 18 years, and they included women and men. Inclusion criteria for HC were: negative medical, psychiatric, and chronic pain history and normal physical examination, including normal neurological exam, and subjects were not taking any analgesic medications. Inclusion criteria for patients with PN were: patients with diagnosis of painful PN following the standard criteria of distal sensory neuropathy, such as sensory deficits or positive sensory phenomena, or both, in lower extremities, worse distally. Exclusion criteria were any acute medical or psychiatric illness, neuropathy, and pain due to causes other than DPN and idiopathic neuropathy in lower extremities. Patients were allowed to continue with all of their medications, including those for pain management and they were instructed to maintain the same dosage prior to testing. University of California, San Diego Institutional Review Board approved the study.

The Testing Protocol

During the study, subjects were comfortably resting in a recliner. Stimulation was first carried out at the foot and then at the hand. DLs stimulation parameters used in this study were based on information from previous preclinical and human volunteer studies, and they were set to elicit reports of “burning pain” which was a psychophysical equivalent to the activation of C-fibers and of “pinprick pain” which was from activation of A-delta fibers [6–8]. Sites of stimulation were the dorsum of the foot and the hand. Stimulation began from 0 mA current, and the current was increased in 100 mA increments until the stimulation was felt as painful. Detection threshold was obtained by applying the method of levels, which consisted of a series of ascending and descending stimuli with 5 up and 5 down changes until the last sensation that was felt as painful. The stimulation protocol for activation for C nociceptors included the 5 mm in diameter area of stimulation, and duration of each stimulus was 2 seconds, and for A-delta nociceptors, diameter was 1 mm and stimulus duration was 60 msec. As per protocol, after each stimulus, the beam of stimulation is moved a few millimeters to avoid buildup of temperature at the same spot of stimulation.

Safety

The past experience with DL demonstrated that stimulation current delivered for up to 3,500 mA for 60 msec for the A-delta protocol and for up to 1,650 mA for 2 seconds for the C-fiber protocol was safe and not producing any observable skin changes [7,8]. Subjects did not report any symptoms during or upon study completion. On the basis of this information and from a previous study, which demonstrated that average surface temperature during stimulation at the very circumscribed area of stimulation with current of stimulation to activate A-delta fibers, limited to 3,500 mA, did not exceed 60°C when stimuli were applied for limited duration of 60 msec and for current of 1,650 mA for 2 seconds did not exceed 52°C, the stimuli described were considered safe for this study [9]. It should be noted that the study by Moritz and Henriques demonstrated that the average stimulation characteristics for temperatures and duration, which did not produce observable injury and therefore deemed to be safe for human skin stimulation, are 100 msec at 65°C and for 2 seconds at 60°C, and our stimulation parameters were distinctly below these published by Moritz and Henriques [11].

Results

Subjects in this study were seven HC, four women, and three men, age of 20–44 (27.6 ± 8.5) years and nine patients with PN, eight of whom had DPN, five women and four men, age of 24–69 (57.6 ± 13.3) years. Patients reported pain only in their lower extremities and provided description of pain in their feet as pins and needles in five patients, as numbness in four patients, as burning in three patients, and as cold, sharp, and cramping in one patient for each of these pain qualities. Spontaneous pain was rated from 2 to 7 (5.3 ± 1.8) on 0–10 scale where 0 is no pain and 10 is worst pain imaginable.

When stimulation was conducted in HC, its intensity required to elicit “burning pain” sensation due to C-fiber activation at the foot of HC was 1,157.71 (±291.33) mA, and intensity required to elicit “pinprick-type sharp pain” sensation due to A-delta fiber activation was 1,638.71 (±377.84) mA (P < 0.05) (Figure 2).

When compared with stimulation intensity required to elicit “pinprick pain” sensation due to A-delta fiber activation at the foot of HC, intensity of stimulation required to elicit A-delta fiber activation at the foot of patients with PN...
was significantly higher, at 2,778.11 (±1,155.32) mA (P > 0.025) (Figure 3), and intensity was also elevated at the hand of patients with DPN, at 2,676.75 (±925.13) mA. Stimulation intensity to elicit “burning pain” sensation at the foot of patients with DPN was 1,238.56 (±250.11) mA, which was not significantly different from the intensity required for eliciting “burning pain” in HC, which was 1,157.71 (±291.33) mA (Figure 3). For patients with PN, stimulation at the hand to elicit “burning pain sensation” was 1,227.67 (±246.18) mA, which was not significantly different from their foot stimulation parameters.

During this study, no subject reported any symptoms once stimulation was completed. Careful observation of the skin of each subject following the completion of stimulation did not reveal and observable skin changes, suggesting that very limited time of stimulation applied to a very limited skin surface produced physiological activation of receptors at nerve terminals without producing any lasting changes in skin structure or its function.

Discussion

This study was built on the previous preclinical and human laboratory studies with DLs, and it reproduced same psychophysical pain sensations of “burning pain” from activation of A-delta fibers and “pinprick sharp pain” from activation of A-delta fiber, both, in HC and patients with PT. Stimulation parameters for those two distinct sensations in our group of HC were clearly different (Figure 2) and consistent with our previous studies. When the same stimulation protocol was applied to patients with clinical manifestations of PN, stimulation intensity requirements were significantly increased for A-delta fiber activation but not for C-fiber activation. This observation would have significant implication regarding the functional status of small fibers in patients with PN, and it is that this differential requirement would point to the fact that A-delta and C-fibers were not affected equally by the disease process that lead to PN, specifically that A-delta fibers were affected by the pathophysiologic mechanisms while C-fibers remained to function without being affected. Observations described in this report are first evidence for such differential effect of PN pathology affecting distinctly differently small peripheral nerve fibers function. Traditionally, all of the small fibers have been studied as one structure, though it was assumed that preferential activation is possible by controlling the nature of the stimulus, such as applying cold vs heat, would activate preferentially A-delta and C-fibers, respectively. However, the nature of those stimulation methods, including contact nature of the thermods, which activate full range of fibers, and the slower ramp of temperature change would lead to much more complex physiology of those fibers, and distinction between the A-delta and C-fibers function was not possible nor specifically pursued.

The main limitation of this study is the small number of patients; however, it should be noted that even with so few patients, it was possible to demonstrate a significant effect. Further studies are necessary to establish performance characteristics of DL in a variety of neuropathies and NP disorders.
Differential activation of small fibers preclinical disease models and human pain disorders will be an important step in bridging the gap in translational pain research. The fact that same DL stimulation parameters used for stimulation of rodents [5,9,10] and human volunteers [7,8] lead to corresponding information, differential activation as demonstrated by single-unit recording by means of electrophysiological recordings in rodents [9] and confirmed by psychophysical reports and LEP in human volunteers about distinct (singular modality) sensations and evoked potential delays [7,8] provides an exceptional opportunity to utilize DL to conduct translational research of pain mechanisms in human health and disease.

References