Conduction velocity of the human spinothalamic tract as assessed by laser evoked potentials

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To study the conduction velocity of the spinothalamic tract (STT) we delivered CO_2 laser pulses, evoking pinprick sensations, to the skin overlying the vertebral spinous processes at different spinal levels from C5 to T10 and recorded evoked potentials (LEPs) in 15 healthy human subjects. These stimuli yielded large-amplitude vertex potentials consisting of a negative wave at a peak latency of about 200 ms followed by a positive wave at a peak latency of about 300 ms. The mean conduction velocity of the STT was 21 m/s, i.e. higher than the reported velocity of the corresponding primary sensory neurons (type II AMH). Because dorsal stimulation readily yields reproducible brain LEPs, we expect this technique to be useful as a diagnostic tool for assessing the level of spinal cord lesions. *NeuroReport* 11:3029–3032 © 2000 Lippincott Williams & Wilkins.

Key words: Conduction velocity; CO_2 laser; Evoked potentials; Mechano-thermal nociceptors; Spinothalamic tract

INTRODUCTION

Radiant heat pulses, generated by a CO_2 laser, excite free nerve endings in the superficial skin layers [1]. Brief suprathreshold pulses directed to the hairy skin evoke pinprick sensations and late brain potentials, both induced by the activation of the type II AMH mechano-thermal nociceptors [2,3]. The afferent volley is conducted by small-myelinated (Aδ) primary sensory neurons and spinothalamic tract (STT) neurons to the brain [4,5]. The main evoked potential arises from deep midline structures, probably the cingulate gyrus [6,7]. Laser evoked potentials (LEPs) allow the assessment of the whole small-fiber pathway [8,9], and have been found abnormal in diseases that damage the peripheral [10,11] or central pathways [4,11,12]. Although proximal limb and dermatomal stimulations have been used in previous studies [13,14], conduction along the human STT has been estimated with distal limb stimulations combined with assumptions of peripheral conduction velocity [15].

In preliminary experiments, we found that laser stimuli to the skin overlying the vertebral spinous processes yielded pinprick sensations at low intensity and readily evoked reproducible scalp potentials. Because stimulation along the spine reduces peripheral conduction to the minimum, we investigated whether dorsal-LEPs could be used to assess conduction along the STT.

MATERIALS AND METHODS

Fifteen healthy volunteers (10 women, five men) aged between 24 and 62 years (mean 33 years) participated in the study. All subjects gave their informed consent and the research was approved by the local Ethics Committee.

Using a CO_2 laser stimulator (Neurolas, Electronic Engineering, Florence, Italy) we delivered brief pulses (wavelength 10.6 μm; beam diameter 2.5 mm; stimulus intensity 1.5–7.5 W, duration 5–15 ms) to the skin overlying the C5 and T10 (10 subjects) or C5, T2, T6, and T10 vertebral spinous processes (five subjects). To avoid habituation, sensitization, and tissue damage, we used long interstimulus intervals (15–30 s) and delivered each laser stimulus at a slightly different skin site, within a transverse 3×1 cm area centered over the spinous process. To assess perceptive thresholds, we delivered series of stimuli at increasing and decreasing intensities; the threshold was defined as the lowest intensity at which the subject perceived at least 50% of the stimuli [16].

In LEP recordings the stimulus intensity was kept at the same intraindividual level (3–4 times the perceptive threshold) at all sites. This intensity evoked strong, but bearable, pinprick sensations and yielded large and stable potentials. Stimuli were delivered in a random sequence to different dorsal skin sites.

Subjects lay prone and were asked to relax their muscles

and stay awake. Skin temperature was controlled and kept constantly above 30°C. White noise through earphones ensured acoustic isolation. Brain electrical activity was recorded (filters 0.5–30 Hz) through silver disc electrodes (impedance $<5\,k\Omega$) from the vertex (Cz) referenced to linked earlobes (A_1A_2). Simultaneous electrooculography monitored ocular movements or eye-blinks. For each site of stimulation two series of 15 artifact-free trials were selected and averaged off-line (Fig. 1). We measured the peak latency of the main negative (N) and positive (P) waves, and the peak-to-peak amplitude.

To estimate the conduction velocity of the STT we used two methods. First, we divided the distance between C5 and T10 by the latency difference of the N-waves at the two sites (15 subjects). Second, we calculated 1/slope of the regression line for all the N-wave latencies obtained at all sites of stimulation along the spine (C5, T2, T6, and T10, 40 sites in 15 subjects; Fig. 1).

Results are given as means ± s.d. Differences between latencies and amplitudes for the various sites of stimulation (having a Gaussian distribution) were evaluated by Student's *t*-test, and those in threshold (not having a gaussian distribution) by Mann-Whitney U-test. Goodness of fit of the linear regression was evaluated with r^2 and its deviation from zero with F-test. For statistics and graphs we used Prism 3.0 (GraphPad, CA, USA).

RESULTS

Perceptive thresholds: Most subjects had the same perceptive threshold in the different sites of stimulation. The mean perceptive threshold was similar at C5 and T10 ($4.4 \pm 2.9\,mJ/mm^2$ *vs* $5.5 \pm 3.6\,mJ/mm^2$; Mann-Whitney: $p > 0.20$).

Laser evoked potentials: In all subjects the laser stimulation to the dorsal skin readily evoked clear and reproducible potentials. The earliest identifiable potential was a negative wave peaking at about 200 ms, followed by a positive wave at about 300 ms (Fig. 1). The evoked potential was often clear in single trials and its peak latency and shape became stable after few averaged trials.

N-wave and P-wave latencies increased significantly from C5 to T10 (N-wave 195 ± 14 ms *vs* 210 ± 15 ms; *t*-test: $p < 0.0001$; P-wave 292 ± 38 ms *vs* 320 ± 33 ms; *t*-test: $p < 0.001$). Conversely, peak-to-peak amplitudes remained unchanged ($10.7 \pm 2.9\,\mu V$ *vs* $10.4 \pm 2.8\,\mu V$; *t*-test $p > 0.50$).

Conduction velocity of the spinothalamic tract: The mean value of the individual STT conduction velocities calculated between C5 and T10 (mean distance 357 ± 36 mm) was 21.16 ± 6.54 m/s. The regression line calculated from the N-wave latencies from all 40 sites of stimulation along the spine indicated a highly significant linear relationship between distance and time ($r^2 = 0.1976$; $F = 9.358$; $p < 0.005$; Fig. 1). The resulting conduction velocity (reciprocal of the slope) was 20.87 m/s. Hence both methods yielded a similar conduction velocity (about 21 m/s).

DISCUSSION

Afferent input and brain signals: Our laser pulses to the dorsal skin evoked pinprick sensations, conveyed by Aδ fibers. The peak latency of the vertex N wave (200 ms)

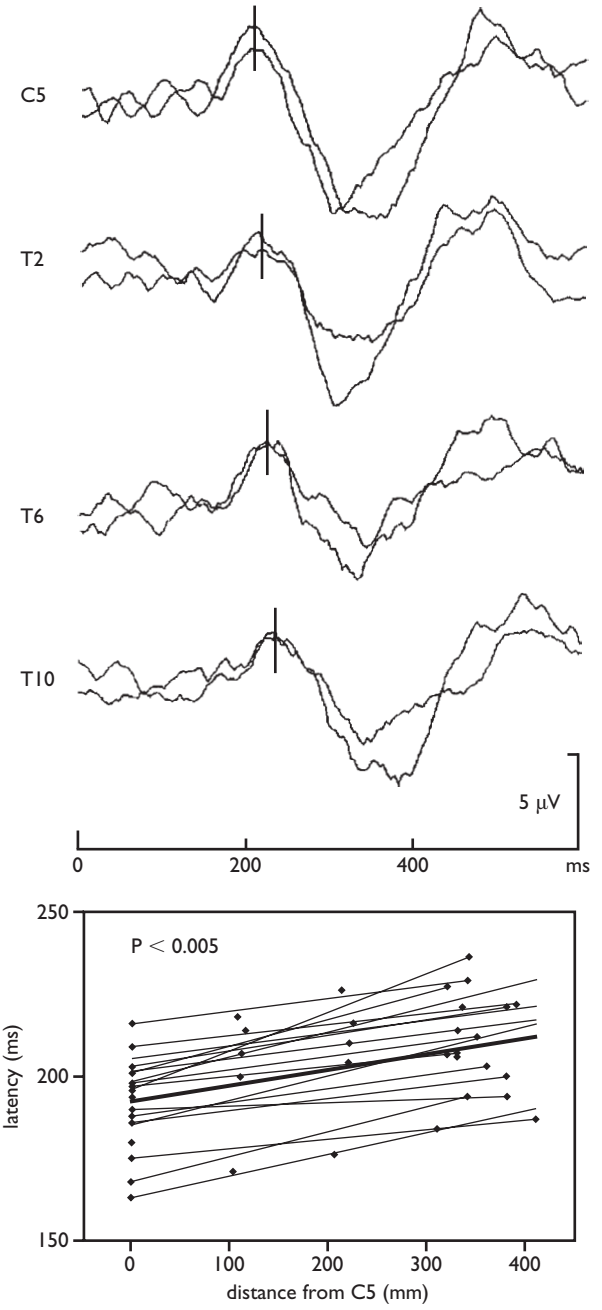

Fig. 1. Upper panel. Laser evoked potentials (LEPs) after stimulation of the skin overlying the C5, T2, T6, and T10 vertebral spinous processes in a 30-year-old normal subject. Negativity upward. The vertical bars indicate peak latencies of the negative components. Two averages (15 trials each) per site of stimulation. Lower panel: Scatterplot and regression of individual latencies in 15 subjects. Y-axis: peak latency of the negative component. Each diamond indicates the peak latency obtained from one site of stimulation. Thin lines were drawn to show intraindividual latency changes: they either represent the individual regressions in the five subjects who had multiple-site stimulations or connect the latencies of the 10 subjects who had the C5 and T10 stimulations. The thick line is the mean regression calculated on all 40 stimulated sites; the reciprocal of the slope of this regression (20.87 mm/ms) indicates mean conduction velocity. Note the widely scattered absolute latencies at C5 (X-axis = 0) whereas the thin lines showing intraindividual latency changes have remarkably parallel slopes.

came between the latencies of the corresponding waves after stimuli delivered to the hand (240 ms) and face (170 ms), with the same laser and recording apparatus [11]. The perceptive threshold was similar to that reported for the perioral region ($\sim$5 mJ/mm^2) but lower than that for the back of the hand ($\sim$12 mJ/mm^2), probably because of differences in receptor density [16,17]. Similarly to LEPs after hand or face stimulation, dorsal LEPs probably originated from activation of type II AMH nociceptors. These neurons have a peripheral conduction velocity of 15 m/s in monkeys [18]. Estimates in humans vary from 9 to 14 m/s [13,19].

The afferent input is relayed to STT neurons in the dorsal horn and reaches the thalamus [4,5,8]. The widespread, high-amplitude scalp potential is generated by deep midline brain structures, probably the cingulate gyrus [6,7]. Although the vertex recording electrode was close to the back area of the primary somatosensory cortex we did not identify earlier waves attributable to the arrival of the signal in the parietal lobe. This is hardly surprising, because after hand or face stimulation, signals earlier than the large and widespread negative component have been identified only with intracortical recordings or after grand-averaging of thousands of trials and dipole source analysis, and originated from the secondary somatosensory area [6,7,20].

Reliability of measurement of spinothalamic tract conduction velocity: Kakigi and Shibasaki [15] estimated a 5.8–9.9 m/s conduction velocity in the human STT. They measured the peak latency of LEPs after hand and foot stimulation, subtracted from these two values the estimated conduction times along the peripheral nerves, thus obtaining an estimate of the central latencies, and attributed the difference between the two central latencies to the time spent along the spinal cord. These calculations could explain why they estimated a conduction velocity < 10 m/s whereas our technique yielded 21 m/s. The discrepancy possibly originated from errors in estimating the peripheral conduction time. First, the measure of the peripheral conduction distance (from the extremities to the entry into the spinal cord) could only be approximate; second, instead of measuring the peripheral conduction velocity in the individual subjects studied, they used the reported data on the conduction velocity of Aδ fibers.

Our dorsal LEP technique has a distinct advantage for measuring spinothalamic tract conduction velocity. It eliminates the need to calculate the peripheral delay for each stimulated site. Not only does the length of the dorsal branches of the spinal nerves and dorsal roots change little between C5 and T10, but the length of the primary neuron is so small (a few centimeters) that possible intraindividual variations in length can be neglected. Furthermore, because of the high receptor density on the skin of the back [16] and the short peripheral distance, laser pulses delivered at relatively low intensities yield scalp potentials that have a higher amplitude and are more stable than those evoked by hand or foot stimulation.

Estimating conduction velocities from LEP latencies has two drawbacks, however. First, because the LEPs recorded from the scalp after stimulations at various sites reflect the peripheral activation of different receptors for each site, to ensure reproducible results stimuli must yield a similar input. We used the same multiples of perceptive threshold, delivered similar energy, elicited similar sensations, and obtained LEPs of almost equal amplitude. Second, the LEP is a late, widespread potential, probably originating from deep midline structures. Whether it reflects the arrival of the nociceptive input at the cortex (cingulate gyrus), or a secondary processing, is unknown. The inherent variability of these signals, and possibly cognitive factors, may influence the latency. We used the same mean frequency of arrhythmic stimulation at different sites and alternated the sites of stimulation, trying to keep the subjects' attentiveness unchanged. The wide interindividual variability in latency probably depended on individual characteristics, including peripheral (receptor times) and central factors (signal processing within brain). But neither of these would affect the measurement of conduction velocity. Indeed, the diagram in Fig. 1 (lower part) shows that, although the absolute latencies were widely scattered, the regression lines for velocity had remarkably parallel slopes.

Support for the STT conduction velocity of 21 m/s we found in human subjects comes from studies in animals, confirming that the conduction velocity of the STT neurons is higher than that of the corresponding primary afferents. In primates, the conduction velocity of nociceptive neurons constituting the STT ranges between 17 and 22.6 m/s [21,22]. Because STT cells have similar anatomical and physiological characteristics in monkeys and humans [23–25], presumably primates and humans have similar STT conduction velocities.

CONCLUSION

The novel finding in this study is that CO_2-laser stimuli delivered to the skin of the human back, because of the high receptor density in this area, readily yield brain evoked potentials probably secondary to excitation of Aδ mechanothermal nociceptors. The estimated conduction velocity of the spinothalamic neurons is about 21 m/s, i.e. higher than the reported velocity of the corresponding primary neurons.

The technique of dorsal LEPs should provide reliable diagnostic information in patients with myelopathy. It may refine the indications for a magnetic resonance imaging study, and if scans are normal could help in assessing the level of a thermal-pain sensory disturbance.

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