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Evidence of different spinal pathways for the warmth evoked potentials

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HIGHLIGHTS

- Conduction velocities of the spinothalamic fibers generating either the C-N1 or the C-P2 LEP components are different.
- Warmth spinal pathways have a parallel organization.
- Warmth has a parallel processing in SII area and cingulate gyrus.

ABSTRACT

Objective: To investigate the presence of multiple spinothalamic pathways for warmth in the human spinal cord.
Methods: Laser evoked potentials to C-fiber stimulation (C-LEPs) were recorded in 15 healthy subjects after warmth stimulation of the dorsal midline at C5, T2, T6, and T10 vertebral levels. This method allowed us to calculate the spinal conduction velocity (CV) in two different ways: (1) the reciprocal of the slope of the regression line was obtained from the latencies of the different C-LEP components, and (2) the distance between C5 and T10 was divided by the latency difference of the responses at the two sites. In particular, we considered the C-N1 potential, generated in the second somatosensory (SII) area, and the late C-P2 response, generated in the anterior cingulate cortex (ACC).
Results: The calculated CV of the spinal fibers generating the C-N1 potential (around 2.5 m/s) was significantly different ($p < 0.01$) from the one of the pathway producing the P2 response (around 1.4 m/s).
Conclusions: Our results suggest that the C-N1 and the C-P2 components are generated by two parallel spinal pathways.
Significance: Warmth sensation is subserved by parallel spinothalamic pathways, one probably reaching the SII area, the other the ACC.

1. Introduction

For a long time, thermal and pain sensations have been considered to be subserved by common pathways both in the peripheral and in the central nervous system. However, a segregation of thermal and noxious inputs has been initially demonstrated at the level of peripheral receptors. Besides the C mechano-heat nociceptors (CMH) and the Aδ mechano-heat nociceptors (AMH), which are activated by painful high-intensity thermal stimuli, the C warm receptors respond optimally to temperatures that are generally perceived as gentle warmth (Darian-Smith et al., 1979; Duclaux and Kenshalo, 1980; Hensel and Iggo, 1971; LaMotte and Campbell, 1978). More recently, separated neurones for thermal and pain sensation have been found in the spinal dorsal horn and in its trigeminal analogous, that is the trigeminal caudalis subnucleus (Han et al., 1998; Craig and Dostrovsky, 2001; Andrew and Craig, 2001). In particular, Andrew and Craig (2001) showed several warm cells within the lamina I, whose threshold is in the range 35–37 °C, and which are supplied by unmyelinated fibers. In human subjects, Iannetti et al. (2003) could measure the conduction velocity of the spinal pathway subserving the warmth sensation, which proved

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slower than the one of the painful input pathway, thus demonstrating the existence of second-order neurons specific for the sense of warmth in man. Dissociation between the conduction velocity (CV) of the spinothalamic fibers belonging to either the Aδ- (painful pinprick sensation) or the C- (warmth) fiber system was found also by Qiu et al. (2001).

The laser evoked warmth potential (C-fiber laser-evoked potentials) recording represents a non-invasive neurophysiological technique for assessing the warm C-fiber pathway from the peripheral receptors up to the cerebral cortex. Microneurographic studies demonstrated that CO_2 laser pulses delivered on the hairy skin activate the thin nociceptive Aδ- and C-fibers selectively (Bromm and Treede, 1984). However, the laser evoked potentials (LEPs) obtained after painful stimulation of the skin show a latency range of 150–350 ms and are generated only by Aδ-fiber inputs (Bromm and Lorenz, 1998). Selective warmth C-fiber stimulation can be obtained by non-painful laser pulses, irradiating a larger skin area (Valeriani et al., 2002, 2005; Iannetti et al., 2003; Cruccu et al., 2003). The C-fiber related LEPs (C-LEPs) include two main components, the earlier of which, labelled as C-N1, is recorded in the temporal region contralateral to the stimulated side; the second one, represented by a biphasic negative–positive complex (C-N2/P2), is obtained on the Cz vertex. Dipole modelling studies of the C-fiber evoked electroencephalographic (EEG) and magnetoencephalographic (MEG) responses suggested that the C-N1 potential is generated in the second somatosensory (SII) area (Opsommer et al., 2001; Ploner et al., 2002; Iannetti et al., 2003; Cruccu et al., 2003; Qiu et al., 2004), while the C-N2/P2 complex, particularly its positive component (C-P2), is originated from the anterior cingulate cortex (ACC) (Ploner et al., 2002; Iannetti et al., 2003; Cruccu et al., 2003; Qiu et al., 2004). As compared to the C-P2 potential, the C-N1 response is less reduced in amplitude by distraction from the laser stimulus, thus it has been linked to the sensory-discriminative component of warmth (Valeriani et al., 2002). On the contrary, the vertex C-LEP components, in particular the C-P2 potential, are extremely sensitive to cognitive factors, e.g. distraction from the warm stimulus (Qiu et al., 2002; Valeriani et al., 2002), and might represent the neurophysiological counterpart of the affective-emotional aspect of warmth experience.

In a previous study (Valeriani et al., 2007), we calculated the CVs of the spinothalamic tracts (STTs) subserving the N1 and P2 components of the painful LEPs, generated by Aδ-fiber inputs, by using an elegant and easy method developed by Cruccu's group (Cruccu et al., 2000; Iannetti et al., 2003). Painful laser pulses were delivered on the skin overlying the vertebral spinous processes at different levels, in order to reduce the peripheral conduction to the minimum (see Iannetti et al., 2001 for a clear description of the advantage of this method over others). In our study, the resulted CVs of the STT fibers generating the N1 and P2 potential were 9 m/s and 13.5 m/s, respectively, thus suggesting that the N1 and the P2 LEP components are generated by two parallel spinal pathways (Valeriani et al., 2007). Our results, together with other neurophysiological findings (Tsuji et al., 2006), supported neuroimaging studies demonstrating that the organization of the spinal nociceptive pathways is parallel, rather than sequential (Hofbauer et al., 2001; Kong et al., 2006; Kulkarni et al., 2005; Schreckenberger et al., 2005). To the best of our knowledge, there is no information about the either parallel or sequential organization of the spinal warmth pathways, although the existence of parallel spinothalamic pathways for warmth may be inferred from the nociceptive system organization.

The aim of the present study was to measure the CVs of the STT fibers generating both the C-N1 and C-P2 potentials, in order to investigate whether the warmth C-fiber inputs, as the nociceptive ones conveyed by the Aδ-fibers, reach the brain through parallel pathways.

2. Methods

2.1. Subjects

Fifteen healthy right-handed subjects (six males, nine females, mean age 28.4 ± 7.3 years), who gave their informed consent, took part in our study. The study conformed to the standards set by the Declaration of Helsinki.

2.2. CO_2 laser stimulation and C-LEP recording

During C-LEP recording, the subjects lay prone on a couch in a warm and semi-dark room. Cutaneous warm stimuli were delivered by a CO_2 laser (10.6 μm wave length, 5 mm beam diameter, 30 ms pulse duration – ELEN, Florence, Italy) on the skin overlying the C5, T2, T6, and T10 vertebral spinous processes. C-LEPs from the different vertebral levels were obtained in separate blocks, which were randomised across all our subjects. The stimulation site was visualized by a He–Ne laser beam. The location of the impact on the skin was slightly shifted between two successive stimuli, to avoid the sensitization of the thermoreceptors. The power of CO_2 laser stimuli was fixed at 4.5 W and all subjects perceived the sensation of a non-painful warmth. In particular, the greatest care was taken that no subject felt pain. The interstimulus interval varied randomly between 9 and 11 s. In 10 subjects, one C-LEP average resulting from 25 to 30 CO_2 laser stimuli was recorded after stimulation of each vertebral level. In order to make the measurement of the latencies of the different C-LEP components more reliable, in the other five subjects two averages, each one of 15 CO_2 laser stimuli, were recorded for each vertebral level stimulation.

In order to make sure that the attention level of our subjects did not change across the whole experiment, they were asked to silently count the number of the received laser stimuli. Averages with a percentage of mistakes higher than 10% were discarded.

C-LEPs were obtained using four recording electrodes placed at the T3, T4, Cz, and Fz positions of the 10–20 International System, and one further recording electrode above the right eyebrow for electrooculogram (EOG) recording. The reference was at the nose, and the ground at Fpz. The EEG signal was amplified and filtered (bandpass 0.3–70 Hz). The analysis time was 1000 ms with a bin width of 1 ms (1000 Hz sampling rate). An automatic artefact rejection algorithm excluded from the average all runs containing transient exceeding ±65 μV at any recording channel, including the EOG.

2.3. Subjective measures

Warmth rating was performed by using a 101-point visual analogue scale (VAS), in which '0' corresponds to no warmth and '100' to the highest conceivable non-painful warmth. After each vertebral level stimulation, the subject was asked to rate the warmth induced by CO_2 laser pulses.

2.4. C-LEP analysis and CV along the spinal cord

C-LEP components were identified on the basis of their latency and polarity. In subjects from whom two C-LEP averages were recorded for each stimulation site, we made sure that both averages overlapped each other without major differences; then the C-LEP components were measured from the calculated mean. The right (rC-N1) and left (lC-N1) C-N1 amplitudes were measured from the baseline in the traces built off-line by referring the temporal electrodes (T3 and T4) to the Fz lead (see later), while the peak-to-peak amplitude was taken into consideration for the vertex biphasic C-LEP component (C-N2/P2).