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SEGMENTAL INHIBITION OF CUTANEOUS HEAT SENSATION AND OF LASER-EVOKED POTENTIALS BY EXPERIMENTAL MUSCLE PAIN

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Abstract—The aim of the study was to evaluate the effect of tonic muscle pain evoked by injection of 5% hypertonic saline in the right brachioradialis muscle on the somatosensory sensation of laser-evoked heat pain and laser-evoked potentials. The heat pain pathways were studied in 9 healthy human subjects by recording the scalp potentials evoked by CO_2 laser stimuli delivered on four sites: the skin above the right brachioradialis muscle (ipsilateral local pain), the wrist area where muscle pain was referred in all subjects (ipsilateral referred pain), and two areas on the left arm symmetrical to both local and referred pain (contralateral local pain and contralateral referred pain). Laser-evoked potentials were obtained from 31 scalp electrodes before saline injection, during saline infusion (bolus injection with 0.3 ml saline infused over 20 s, followed by a steady infusion rate of 30 ml/h for the next 25 min), and 20 min after muscle pain had disappeared. While the early N1/P1 component (around 130 ms and 145 ms of latency after stimulation of the skin over the brachioradialis muscle and the wrist, respectively) was not affected by muscle pain, the amplitudes of the later vertex laser-evoked potentials (N2 latency of around 175 ms and 210 ms after stimulation of the skin over the brachioradialis muscle and the wrist, respectively; P2 latency of around 305 ms and 335 ms after stimulation of the skin over the brachioradialis muscle and the wrist, respectively) evoked from ipsilateral local pain, ipsilateral referred pain, and contralateral local pain sites were significantly decreased during muscle pain compared with the baseline recording, while they recovered after pain had disappeared. At the same stimulation sites, the rating of the laser-evoked pain sensation was reduced significantly during muscle pain as compared with the baseline and it recovered after pain had disappeared. On the contrary, muscle pain did not show any effect on both laser-evoked pain and laser-evoked potential amplitude when the contralateral referred pain site was stimulated. The muscle pain inhibitory effect on both heat pain sensation and laser-evoked potential amplitude is probably mediated by an ipsilateral and contralateral segmental mechanism which acts also on the referred pain area, while more general inhibitory mechanisms, such as a distraction effect or a diffuse noxious inhibitory control, are excluded by the absence of any effect of muscle pain on laser-evoked pain and laser-evoked potentials obtained from a remote site, such as the contralateral referred pain area. Since muscle pain induced by hypertonic saline injection is very similar to clinical pain, our results can be useful in understanding the pathophysiology of the somatosensory modifications which can be observed in patients with musculoskeletal pain syndromes. © 2005 Published by Elsevier Ltd on behalf of IBRO.

Key words: referred pain, local pain, CNS, spinal cord.

Musculoskeletal pain disorders are very common in clinical practice and are often characterized by changes in somatosensory sensation. These modifications occur not only in the site of the lesion causing pain (local pain), but also in painful areas without tissue pathologies (referred pain) and even in non-painful regions (Graven-Nielsen and Arendt-Nielsen, 2003). Many studies in patients with musculoskeletal pain and in healthy subjects in whom muscle pain was induced experimentally investigated how muscle pain interferes with somatosensory sensations of different modalities. The results are often in disagreement, depending on several factors, such as the pain timing and intensity, the explored body region and the way in which the somatosensory modality is studied. In particular, the effect of muscle pain on cutaneous heat sensation is controversial, it being increased (hyperalgesia) according to some authors (Leffler et al., 2000a,b; Tuveson et al., 2003) or reduced (hypoalgesia) in other articles (Graven-Nielsen et al., 1997a; Romaniello et al., 2002; Sluka, 2002; Tuveson et al., 2003). In the present study, we aimed at investigating two open issues. First, the modification of the heat pain in the areas of both local and referred tonic muscle pain was examined during the induction of muscle pain and after its disappearance. Referred pain is probably a central mechanism because it is possible to induce referred pain to limbs with complete sensory loss due to spinal injury (Whitty and Willison, 1958) or to an anesthetic block (Feinstein et al., 1954). Therefore, we might expect that cutaneous pain sensation in the area of referred pain is affected due to the complex interactions underlying the referred pain origin. Second, we investigated the heat pain sensation in symmetrical non-painful regions contralateral to local and referred pain, in order to show the general or segmental character of the muscle pain–heat pain interaction.

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Abbreviations: ANOVA, analysis of variance; BM, brachioradialis muscle; CLP, contralateral local pain; CRP, contralateral referred pain; DNIC, diffuse noxious inhibitory control; EOG, electrooculogram; ILP, ipsilateral local pain; IRP, ipsilateral referred pain; LEP, laser-evoked potential; MDvc, ventral caudal portion of the medial dorsal nucleus; VAS, visual analog scale; VMpo, posterior part of the central medial nucleus.

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To achieve our aim, we assessed the heat pain by measuring the subjective pain sensation induced by CO_2 laser pulses and by recording the scalp laser-evoked potentials (LEPs). The study of the scalp LEPs offers a unique opportunity to explore non-invasively the nociceptive pathways, from the transduction of the painful stimulus into neural signals up to the transmission of the nociceptive inputs and their cerebral processing. Indeed, microneurographic studies demonstrated that CO_2 laser pulses delivered on the hairy skin activate specifically the thin nociceptive Aδ and C fibers, without any concurrent stimulation of the non-nociceptive Aβ afferents (Bromm and Treede, 1984). In particular, LEPs obtained after painful stimulation of the hand skin show a latency range of 150–400 ms and are generated by Aδ-fiber inputs (Bromm and Lorenz, 1998). In this study muscle tonic pain was induced by injection of hypertonic (5%) saline. As it has been demonstrated (Stholer and Lund, 1994; Svensson et al., 1995; Graven-Nielsen et al., 1997a), this is an effective and standardized method of evoking tonic, fully reversible muscle pain in humans, by stimulating both the Aδ and C muscular fibers (Mense, 1993). Since the quality of the saline-induced pain is comparable to clinical pain (Kellgren, 1938; Stohler and Lund, 1994), further knowledge about how tonic muscle pain interacts with heat pain could result in better understanding of the somatosensory modifications in chronic musculoskeletal pain syndromes.

EXPERIMENTAL PROCEDURES

Subjects

Nine healthy right-handed subjects (four males, five females, mean age 32.3±5.3), who gave their informed consent, took part in our study. Muscle pain was induced by saline injection in the right brachioradialis muscle (BM).

CO_2 laser stimulation and LEP recording

During LEP recording, the subjects lay on a couch in a warm and semi-dark room. Cutaneous heat stimuli were delivered by a CO_2 laser (10.6 μm wave length, 2 mm beam diameter, 10 ms pulse duration; ELEN, Florence, Italy) to the right and left arm. On the right arm, LEPs were recorded after stimulation of the skin overlying the BM (ipsilateral local pain, ILP) and on the lateral dorsum of the wrist (C6 dermatome), where pain is usually referred after saline injection in BM (ipsilateral referred pain, IRP). Symmetrical cutaneous areas to ILP and IRP were stimulated on the left arm (contralateral local pain—CLP—and contralateral referred pain, CRP). 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 nociceptors. In all the experimental phases (see below), CO_2 laser stimuli were fixed at 18 mJ/mm^2, which was clearly painful. All our subjects felt the CO_2 laser pulses as painful pinpricks in all trials. Averaged LEPs resulted from 25 to 30 CO_2 laser stimuli.

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

LEPs were obtained using 32 recording electrodes, 31 of which placed according to the positions of the 10–20 International System (excluding Fpz and Oz), and the remaining one above the right eyebrow for electrooculogram (EOG) recording. The reference was at the nose, and the ground at Fpz. The electroencephalographic (EEG) signal was amplified and filtered (bandpass 0.3–70 Hz). The analysis time was 1000 ms with a bin width of 2 ms (500 Hz sampling rate). An automatic artifact rejection algorithm excluded from the average all runs containing waves of amplitude exceeding ±65 μV at any recording channel, including the EOG.

LEP analysis

In this study, the LEP components evoked by painful stimulation of the skin showed a latency consistent with their generation by Aδ fiber inputs (Bromm and Lorenz, 1998). LEP components were identified on the basis of their latency and polarity by two authors (L.D.A. and T.M.) who were blind to study design. LEPs were labeled according to Valeriani et al. (1996). LEP amplitudes were measured from the baseline. Also the peak-to-peak amplitude was taken into consideration for the vertex biphasic LEP component (N2a-P2). For the analysis of LEP distribution, color maps calculated by spline interpolation (Perrin et al., 1987) were used. Grand-averages of LEPs recorded in the different conditions after stimulation of all sites (ILP, IRP, CLP, and CRP) were obtained for demonstrative purposes.

Experimental muscle pain

The injection of 5% hypertonic saline in the right BM was carried out by a pump. A tube was connected from the pump to the disposable stainless needle. A standardized bolus injection with 0.3 ml saline was initially infused over 20 s, followed by a steady infusion rate of 30 ml/h for the next 25 min (modified from Graven-Nielsen et al., 1997a).

Experimental procedure

LEP recording. LEPs were recorded at three times: (1) before saline injection (pre-injection recording), (2) from 5 min up to 25 min after saline injection beginning (injection recording) and (3) 20 min after muscle pain disappearance (post-injection recording). In each of the experiment times, LEPs were recorded after stimulation of the ILP, IRP, CLP, and CRP sites and the order of the different recordings was randomly changed across the subjects.

Psychophysics. Pain rating was performed by using a 100-point visual analog scale (VAS), in which "0" corresponds to no pain and "100" to the worst pain one may conceive. After each LEP recording the subject was asked to rate the pain induced by CO_2 laser pulses (laser pain). Muscle pain intensity was assessed every 5 min after the start of the infusion, until pain disappeared.

Statistical analysis

For psychophysical tests, the pain ratings were compared by one-way ANOVA (analysis of variance) with repeated measures, by considering the rating time as the variable. If statistical significance was reached, post hoc analysis was performed by paired *t*-test.

The LEP latencies across the different times were compared by two-way ANOVA with repeated measures, by considering the recording time and the recording electrode as the variables. For LEP amplitude comparison, LEP amplitudes obtained in injection and post-injection recordings were expressed as percentages of the amplitudes of the corresponding LEP components obtained from pre-injection recording on the same stimulation site, which were assumed as 100%. After this normalization, amplitudes were compared by two-way ANOVA with repeated measures, by considering the recording time and the recording electrode as the variables. If statistical significance was reached, post hoc analysis was performed by paired *t*-test.