Painful Stimuli Evoke Potentials Recorded Over the Human Anterior Cingulate Gyrus

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F. A. Lenz, M. Rios, A. Zirh, D. Chau, G. Krauss, and R. P. Lesser. Painful stimuli evoke potentials recorded over the human anterior cingulate gyrus. J. Neurophysiol. 79: 2231–2234, 1998. Clinical studies of cingulotomy patients and imaging studies predict that the human cingulate gyrus might display pain-related activity. We now report potentials evoked by painful cutaneous stimulation with a CO₂ laser (LEP) and recorded from subdural electrodes over the medial wall of the hemisphere. In response to facial laser stimulation on both sides, a negative (latency 211–242 ms) and then a positive wave (325–352 ms) were recorded from the cortex of right medial wall and from the falx dura overlying the left medial wall. Medial wall LEPs were similar to scalp LEPs and were largest over the anterior cingulate and superior frontal gyri just anterior to motor cortex contralateral to the side of stimulation. These results demonstrate that there is significant direct nociceptive input to the human anterior cingulate gyrus (Brodmann’s area 24).

INTRODUCTION

The role of anterior cingulate cortex in human pain perception is suggested by the relief of intractable pain can result from lesions in this area (Folz and White 1962; Hurt and Ballantine 1973). Positron emission tomogram (PET) studies consistently report metabolic activation of cingulate gyrus by painful stimuli (Casey et al. 1994; Coghill et al. 1994; Craig et al. 1996; Talbot et al. 1991; Vogt et al. 1996). Short-duration cutaneous stimulation with a CO₂ laser evokes pain-related cerebral potentials (LEPs) (Bromm and Treede 1984; Carmon and Treede 1978) with a vertex maximum (Beydoun et al. 1993; Bromm and Treede 1984; Kunde and Treede, 1993; Tarkka and Treede, 1993) because of selective activation of cutaneous nociceptors (Bromm and Treede 1984). It has been suggested that the vertex maximum of the LEP arises, in part, from generators in the cingulate gyrus (Chen and Bromm 1995; Kitamura et al. 1995; Tarkka and Treede 1993; Valerianai et al. 1996). We now report direct evidence of nociceptive inputs to the human cingulate gyrus, which may contribute to the vertex LEP.

METHODS

These studies were carried out at Hopkins Hospital in five patients with epilepsy. Subdural potentials were studied in a 24-yr-old man with complex partial seizures from a suspected medial frontal lobe focus; he was neurologically intact. Subdural grids were placed bilaterally over the convexity and the medial wall of the hemisphere (see Fig. 1) for investigation of his epilepsy. One side of the electrode grid faced the cortex of the right medial wall; the other side faced falx dura overlying the left medial wall. Electrodes on the medial wall were referenced to a subdural electrode over the right occipital convexity. Because scalp electrodes could not be applied with the grid in place, scalp LEPs were recorded during scalp monitoring of the other four patients. None of the five patients had abnormalities on the magnetic resonance imaging scan (MRI); all gave informed consent under a protocol approved by the Hopkins Institutional review board.

The patients were alert, wore protective lenses, and lay in a reclining position. Cutaneous heat stimulation was delivered by a CO₂ laser (LX-201, Luxar corporation, Bothell, WA; pulse duration, 20 ms; wavelength, 10.6 μm; beam diameter, 6 mm). The stimulus was delivered from a distance of 4 cm above the skin at an intensity of 10–13 W/mm², which evoked pain (3–4/10, visual analog scale). At these parameters, a component of mechanical, warm or heat sensation was never reported spontaneously or in response to direct questioning (see also Bromm and Treede 1984; Carmon et al. 1978). Successive stimuli were applied at slightly different locations, to avoid sensitization, and at pseudorandom intervals (5–7 s). During recordings white noise was continuously delivered to both ears (Click-tone module, Grass Instruments, Quincy, MA).

Subdural LEPs were recorded from a cartesian grid of circular platinum-iridium electrodes (2.3 mm diam) embedded at 1-cm intervals in a clear silastic sheet with one electrode facing each surface of the sheet (Ad-Tech Corp, Racine, WI, USA). Electrode location (Fig. 1) was determined by intraprocedural photographs and by superimposition of 3D computerized tomographic data (for electrode location) on the 3D MRI (for gyral anatomy, see Fig. 1 in Boatman et al. 1997), as confirmed by stimulation mapping. Stimulation mapping through adjacent grid electrodes was performed as previously described (2–5 s train, 50 Hz, 0.3 ms pulses of alternating polarity) (see Lesser et al. 1994), which produced excitation at both of the stimulated electrodes (Ranck 1975). Movements were evoked by stimulation of electrodes on the medial wall (Fig. 1) at current ≤1 mA. In the patients studied by scalp recordings, 13 disc electrodes were placed in standard configuration (International 10-20 system with linked ears) (Jasper 1958).

Electroencephalographic (EEG) recordings were obtained (Grass Model 12 amplifiers, bandpass: 0.1–100 Hz; gain: 5000) with electrode impedance as follows: scalp < 5 kΩ, subdural < 20. Signals were digitized (scalp: 256 Hz, grid: 512 Hz) from 200 ms before stimulus onset to 1 s after. Individual trials that were free of artifact were included in averages of 20–35 trials and two or more averages were compared to assess reproducibility (Fig. 2). For reproducible waveforms, peak latencies and amplitudes (baseline to peak) of each component were measured from the grand average of 40–70 trials (Fig. 1). Separate averages were taken for stimulation of each side of the face (V2/V3) and of the dorsum of the hand. LEPs in the present results and in the literature (Beydoun et al. 1993; Chen and Bromm 1995; Kitamura et al. 1995; Kunde and Treede 1993; Tarkka and Treede 1993; Valerianai et al. 1996) were termed N2 for the largest negative wave and P2 for the largest positive wave because stimulation and recording techniques were practically identical in all these studies.
RESULTS

LEPs were recorded from electrodes on the cortex of right medial wall and the falcine dura overlying the left medial wall. On either side LEPs recorded from the medial wall consisted of a negative wave (N2) followed by a positive wave (P2, Fig. 2). These were reproducible after facial stimulation but were not acceptably reproducible after hand stimulation. Averaged recordings of the maximal right subdural LEPs (top) and scalp LEPs (bottom) in response to stimulation of the face have been shown in Fig. 1. LEPs recorded from medial wall after contralateral facial stimulation consisted of N2 (right medial wall amplitude, 50 μV) followed by P2 (38 μV), with latencies as shown in Table 1. LEPs from the right hemisphere after ipsilateral facial stimulation (Fig. 2, ipsi maxima) had a maxima at the same location as for contralateral stimulation and similar morphology and latency, but amplitude was <75% of that after contralateral stimulation. In response to stimulation of the right face the maximal LEP on the left medial wall was at the same electrode as the maxima on the right medial wall in response to stimulation of the left face (Fig. 1). Potentials for contra- and ipsilateral stimulation were smaller on the left medial wall than the corresponding potentials on the right, presumably because of attenuation by the falx. Scalp LEPs were measured bilaterally in four epileptic patients (1 male, 3 females, ages 33–43). Scalp LEPs had overlapping latencies with (Table 1) and morphology similar to subdural LEPs (Fig. 2). The scalp N2 had a vertex maximum (Cz, 10 μV) and scalp P2 had a maximum (14 μV) at Pz, which is a point located at 40% of distance from the vertex to the inion (Jasper 1958).

Subdural LEPs from contralateral facial stimulation have been shown as a function of position of the recording electrode on the right medial wall in Fig. 1. The central sulcus was defined relative to the marginal branch of the cingulate sulcus (MCIIS) and confirmed by stimulation mapping (see METHODS). LEPs were broadly distributed with maxima over the anterior cingulate and superior frontal gyri 3 cm anterior to the central sulcus.

DISCUSSION

This report demonstrates that painful cutaneous laser stimulation evokes reproducible potentials over the medial wall of the hemisphere. These potentials are maximal over contralateral anterior cingulate and supplementary motor areas. Potentials over the medial wall ipsilateral to the site of stimulation are smaller, which suggests that the ipsilateral projection mediating these potentials is weaker than the contralateral projection (Sikes and Vogt 1992). Short duration cutaneous laser stimulation evokes both pain and cerebral potentials because of selective activation of nociceptors (Bromm and Treede 1984; Carmon et al. 1978). Therefore, the present findings demonstrate that human anterior cingulate gyrus receives significant bilateral input arising from nociceptors.

Laser stimulation of the hand evokes scalp potentials with a symmetrical distribution, vertex maximum, and with both N2 (214–248 ms) and P2 components (335–390 μV) (Beydoun et al. 1993; Bromm and Treede 1984; Kunde and Treede 1993; Tarkka and Treede 1993). Scalp N2 (150 μV) and P2 (230 μV) components occur at shorter latency after stimulation of the face (Kazarians et al. 1995). Differences between scalp and subdural potentials (Table 1) may occur because scalp LEPs result from other generators in addition to the cingulate gyrus (Chen and Bromm 1995; Tarkka and Treede 1993) or because of variation between subjects (Beydoun et al. 1993; Kazarians et al. 1995).

Figure 1 shows a clear increase in potentials as electrode position approaches the maxima (potential above the CC label for corpus callosum) from posterior, anterior, and superior, suggesting that the generator is adjacent to the maxima. The maxima is found at the same electrode in two hemispheres, suggesting that the generator is found at a constant anatomic locus in this patient, at least. However, six large potentials are found around the maxima on the medial wall. This suggests that LEPs are less localized than the shorter latency potentials recorded over sensorimotor cortex on the medial wall in response to electrical stimulation of the posterior tibial nerve (Lesser et al. 1987). Late potentials are...
TABLE 1. Latencies of LEPs evoked by facial stimulation and recorded from electrodes on the contralateral medial wall of the hemisphere and on the scalp

<table>
<thead>
<tr>
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<th>Medial Wall Maxima, ms</th>
<th>Cz</th>
<th>C3-C4</th>
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<tr>
<td>N2</td>
<td>211–242</td>
<td>182 ± 19</td>
<td>184 ± 18</td>
</tr>
<tr>
<td>P2</td>
<td>325–352</td>
<td>281 ± 38</td>
<td>281 ± 37</td>
</tr>
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Values are mean LEPs ± SE. Number of observations for medial wall maxima was 2, for Cz was 8, and for C3-C4 LEPs was 8. In each patient studied, results were recorded from two hemispheres (medial wall and C3-C4) in response to contralateral stimulation or from the vertex (Cz) in response to stimulation of either side of the body. LEPs, laser-evoked potentials.

...gyrus (Kakigi et al. 1995; Kitamura et al. 1995). The generators of these currents may be cells in cingulate gyrus, which respond to nociceptive inputs (Hutchinson et al. 1993; Sikes and Vogt 1992).

...Painful thermal stimuli produce metabolic activation (PET) of ipsilateral (Vogt et al. 1996) plus contralateral anterior cingulate gyrus (Casey et al. 1994; Coghill et al. 1994; Craig et al. 1996; Talbot et al. 1991; Vogt et al. 1996), primary and secondary somatosensory areas, insular cortex (Casey et al. 1994; Coghill et al. 1994), and supplementary motor area. The present results suggest that nociceptive inputs (latency 211–242 ms) may well be involved in metabolic activation of the cingulate gyrus bilaterally. However, other mechanisms may account for the increase in activation that is observed when the affective component of pain increases (Rainville et al. 1997).

...Lesions of anterior cingulate gyrus produce relief of chronic pain in 23% (Hurt and Ballantine 1973) to 75% of patients (Folz and White 1962). These lesions (>2 cm diam) (Hurt and Ballantine 1973) are centered in the cingulate gyrus 1–3 cm posterior to the genu of the corpus callosum (Folz and White 1962; Hurt and Ballantine 1973) and so include the LEP maxima (Fig. 1). After cingulotomy, patients with chronic pain report that they continue to have pain, which is “not particularly bothersome” (Folz and White 1962). Thus the present results demonstrate that the human anterior cingulate gyrus (Brodmann’s area 24) receives direct nociceptive inputs, which account, in part, for the results of previous LEP, magnetoencephalographic, PET, and lesion studies.

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