Cold Stimuli Evoke Potentials That Can Be Recorded Directly From Parasylvian Cortex in Humans

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INTRODUCTION

The cortical structures that mediate the sensation of cold in humans have not been clearly identified. Imaging studies have implicated contralateral sensorimotor cortex, S2, premotor cortex, anterior cingulate cortex, and insula in innocuous cold sensations (Casey et al. 1996; Craig et al. 2000; Davis et al. 1998; Kim et al. 2007). Some of these cortical areas receive input from thalamic nuclei containing neurons that respond to cold stimuli in monkeys and humans (Davis et al. 1999; Lee et al. 1999; Lenz and Dougherty 1998b). Stimulation in the region of the human thalamic somatic sensory nucleus (ventral caudal [Vc]) at microampere currents (microstimulation) can evoke the sensation of cold (Davis et al. 1999; Ohara and Lenz 2003). Subnuclear thalamic lesions in humans or injections of local anesthetic in monkeys decrease perception of cold stimuli (Duncan et al. 1993; Kim et al. 2007).

There is scant evidence of cortical electrical events evoked by cold stimuli, which constitute basic evidence to identify cortical structures mediating the sensation of cold. A study of cold evoked potentials (cold EPs) from scalp electroencephalograms (EEGs) (Duclaux et al. 1974) demonstrated potentials with a maximum at the scalp location C4, possibly corresponding to the location of sensorimotor cortex (Jasper 1958).

We have now tested the hypothesis that parasylvian cortical structures display evoked responses to cold stimuli. We recorded the response to cold stimuli from electrodes implanted directly over parasylvian cortex for the investigation of complex partial seizures of temporal lobe onset. The results demonstrate that cold EPs can be recorded consistently over structures adjacent to the Sylvian fissure.

METHODS

This study was carried out at the Johns Hopkins Hospital between 2005 and 2006. The study protocol was approved by the Institutional Review Board of the Johns Hopkins University and the University of Maryland. All patients signed an informed consent for inclusion in these studies. These protocols were carried out in two female patients, 40 and 26 yr of age, who had subdural grids implanted for surgical treatment of medically intractable complex partial seizures in the absence of generalized seizures or previous brain surgery. The grids were implanted over left frontal, parietal and temporal cortex including the region shown in Fig. 1B (patient 1102).

Seizures in patient 1102 were treated chronically with phenobarbital (60 mg once per day) and lamotrigine (225 mg twice per day). Patient 1122 was treated chronically with oxcarbazepine (1,200 mg in the morning; 1,050 mg in the evening) and zonisamide (300 mg twice per day). Both patients had been off these medications for ≥24 h at the time of this testing. The half-life of these drugs is in the range of 14 to 24 h in patient 1102 and 14 to 60 h in patient 1122, so that both patients had substantial drug levels at all time points relevant to this study (PDR 2008).

Both patients were on a standard neurological examination, including a sensory testing protocol, disclosed no abnormality (Adams et al. 1996; Lenz et al. 1993b). Brain magnetic resonance imaging (MRI) revealed no abnormality in patient 1102 and mesial temporal atrophy in patient 1122, which is consistent with the diagnosis of temporal lobe epilepsy, but not with sensory abnormalities (Adams et al. 1996; Gloor 1997).

As a part of the sensory protocol sites on the face, the dorsum of the hand, and the foot were stimulated with a battery of stimuli including: camel hair brush, brass probe at room temperature (23°C), brass probe kept in ice water, plastic probe at room temperature, and tuning fork (128 Hz) (Essick 1992; Kim et al. 2007; Lenz et al. 1993b). The description of these stimuli using a standard questionnaire was examined to determine whether responses were different from those determined in a population of patients with movement disorders and no identified sensory abnormality (Lenz et al. 1993b). By this protocol neither patient had any abnormality of cold sensation, although the protocol provides only an approximate measure of sensory function (Lenz et al. 1993b).

Standard techniques were used to identify cortical gyri and sulci from the three-dimensional MRI scan (Boatman et al. 1997; Lenz et al. 1998a; Vogel et al. 2003). The central sulcus (CS) was identified relative to both the deep symmetrical, approximately medial–lateral
sulcus with the inverted omega sign on axial scan (Fig. 1B), and the marginal branch of the cingulate sulcus (not shown) (Lenz et al. 1998b; Naidich et al. 1995). The CS was also identified by the inferior frontal gyrus (IFS, Fig. 1B) and superior frontal sulcus (SFS, Fig. 1B), each of which forms a T-junction with the precentral sulcus (PreCS, Fig. 1B). The postcentral sulcus (PostCS, Fig. 1B) and sylvian fissure (SF, Fig. 1B) are also labeled (Naidich 1991; Naidich et al. 1995).

This anatomy was confirmed by intraoperative photos of electrode position relative to the cortical structures as determined by an intraoperative computerized guidance system (Brainlab, Munich, Germany).

The cold stimulus was produced by a system of temperature-controlled water baths and pumps. This cold stimulator was constructed at the University of Maryland Dental School (JD Greenspan). It consisted of three water baths (Neslab RTE-111), each of which held 7.0 L of water, and could be set to maintain any given temperature between −25 and 100°C with 0.1°C stability. Each bath was outfitted with a suction pump (LC 3CP MD; March Manufacturing), capable of pumping 32 L/min. Water from each bath was directed through insulated Tygon tubes to a switching station. The switching station allowed for each bath’s water flow to be directed either 1) back to the same bath directly or 2) to the stimulator head before returning to the same bath. For this experiment, only two different temperatures were required: 31 and 5°C.

The stimulator itself was a flat copper conduit with a stimulator surface of 1.5 × 4 cm that was placed on the skin. This copper piece

FIG. 1. Potentials recorded directly from the brain in response to a nonpainful cold stimulus applied to the contralateral hand. A, top: the profile of the average temperature stimulus. Bottom: the maximal potential recorded over the parietal operculum in subject 1122. B: the location of electrodes in subject 1102. Evoked potentials (EPs) recorded from the 3 rows of electrodes labeled C, D, and E in B are shown in C, D, and E. Electrodes in these 3 rows are numbered from 1 to 6 in B and EPs recorded from those electrodes in any row are also numbered from 1 to 6, as appropriate. Overlays of potentials recorded from 2 adjacent electrodes with large EPs for each row are shown as the bottom tracing in the corresponding C, D, and E.
was 0.5 mm thick, so as to rapidly conduct the temperature from the circulating water to the skin’s surface. The temperature at the probe surface–skin surface was monitored using a PhysiTemp (Clifton, NJ) IT-1E thermister, capable of measuring temperatures accurate to 0.1°C, with a time constant of 5 ms. The output of that thermister signal was sent as an analog input signal recorded along with the local field potential (LFP) signals from the cortex.

The skin was maintained at an adapting temperature of 31°C prior to the cold stimuli. The water flow to the stimulator was manually switched from a water bath at 31°C to flow from the refrigerated water (5°C). The cooled water was directed through the stimulator for 2 s before being switched back to the output of the 31°C water bath (Fig. 1). Between 1 and 3 min was allowed between successive stimuli. With each stimulus, the stimulator was moved to a different location on the dorsum of the hand or forearm contralateral to the grid electrodes.

LFPs were recorded from 64 subdural electrodes whose properties and location of were as previously described (Ohara et al. 2004). Multichannel LFP signals were remontaged using an average reference to minimize the influence of location and activity of the reference electrode (Crone et al. 1998; Lehmann 1987). The time of onset of the cold stimulus was determined by the first change in temperature as determined by visual inspection of the temperature trace (Fig. 1A) (Ohara et al. 2001). Evoked potentials were averaged across cold stimuli zeroed to the first change in temperature.

A time window of 2.1 s with 0.1-s prestimulus period was used for the cold EPs. Responses to individual trials with artifacts or large baseline fluctuation were excluded before averaging. A total of 30–50 responses were used for averaging. Peak latencies and amplitudes were measured from averaged waveforms. Peak amplitudes were measured from the baseline value, defined as the average value during the prestimulus period. All latencies were measured at the time of peak amplitude. Descriptive statistics are given as means ± 1SD; differences between parametric variables were tested with t-tests and tests of proportions included Fisher or chi-square, as appropriate.

RESULTS

Figure 1A shows the temperature trace (top) and one EP in the same timescale used in Fig. 1, C, D, and E. The temperature of the conduit was dropped from an average adapting temperature of 31°C to approximately 27°C within 0.5 s, and to 21°C within 2 s. The variance of the temperature signal increased progressively from the onset of the stimulus to the temperature nadir. Both patients described this stimulus as a nonpainful, surface, cold sensation. LFP recordings in both subjects demonstrated a slow negative potential over the frontal and parietal lobes in response to this stimulus. The maximal evoked potential for subject 1122 is shown in Fig. 1A (bottom).

Locations of the electrodes in subject 1102 are shown in Fig. 1B, whereas the EPs for this subject along the same rows of electrodes are shown in Fig. 1, C, D, and E, as appropriate. The recordings from the frontoparietal lobe (Fig. 1C) showed slow negative potentials, whereas those over the temporal lobe were positive (Fig. 1, D and E). In patient 1122 EPs were all negative and recorded only over the frontoparietal lobe.

Table 1 shows peak amplitudes and maxima for negative waves (subjects 1102 and 1122) and positive waves (subject 1102 only). Peak amplitudes were calculated from all electrodes for which EPs were recorded, as indicated by n. Peak amplitudes were about 30 μV and occurred at a latency of about 800 ms (Table 1). Differences between patients 1102 (Fig. 1, B–E) and 1122 (maximum shown in Fig. 1A) were significant for amplitudes (P = 0.021, t-test), but were not significant for latency (P = 0.35, t-test).

In subject 1102, negative potentials were recorded from the row of electrodes on the frontal and parietal lobes as shown in Fig. 1C. Positive potentials were recorded in the two rows of electrodes over the temporal lobe in Fig. 1, D and E. It is notable that the mean latencies of the positive waves below the sylvian fissure and negative waves above the fissure are identical (Fig. 1) in this patient, suggesting that they are produced by the same generator. Spatial reproducibility of the response over cortical recording from electrodes separated by 1 cm are shown in the overlays located in the bottom row of C, D, and E. It seems unlikely that volume conduction explains these results since the slow waves are reproducible, whereas the noise is different, particularly in C and E.

DISCUSSION

Overall, the peak of the cold evoked potentials occurred with a mean amplitude of 30 μA and a latency of about 800 ms. This is consistent with the late response to cold stimuli, which occurs in human thalamic neuronal activity (Lenz and Dougherty 1998). In a previous study of scalp cold evoked potentials (Chatt and Kenshalo Sr. 1979) the peak latency was 325 ms, which is much shorter than the present results. One major difference between the previous scalp EEG study and the present study is that the earlier scalp study apparently achieved a faster rate of temperature change, thereby producing faster and more robust activation of afferents responding to cold stimuli. At the same time, rapid cooling of the skin evokes mechanoeceptor activation (Burton et al. 1972; Duclaux et al. 1974), which may be the source of the higher-velocity inputs and the shorter EP latencies in the scalp study. The location of the maximum cold evoked response in the Duclaux et al. study was at contralateral C4, possibly corresponding to the location of the sensorimotor cortex (Jasper 1958). This also suggests mechanoeceptor activation in the scalp study since sensorimotor cortex is the primary cortical locus for mechanoreceptive input.

Localization of the generators of evoked potentials by subdural recordings is more reliable than that by scalp recordings. When event-related potentials are recorded from the scalp, they are limited by low-pass and spatial filtering at the scalp, skull, and CSF (Cooper et al. 1965; Gevins et al. 1994; Pfurtscheller and Cooper 1975), and by large interelectrode distances (Gevins et al. 1994). The present subdural recordings avoid all these sources of error and clearly indicate that cold evoked

**TABLE 1. Latency and amplitude for cold evoked potentials (EPs) in the two subjects studied in this report**

<table>
<thead>
<tr>
<th>Subject Identifier</th>
<th>Latency, s</th>
<th>Amplitude, μA</th>
<th>Amplitude Maxima Among Recorded EPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1122: negative potentials (n = 6)</td>
<td>0.92 ± 0.08</td>
<td>24 ± 5</td>
<td>−31</td>
</tr>
<tr>
<td>1102: negative potentials (n = 9)</td>
<td>0.80 ± 0.10</td>
<td>39 ± 10</td>
<td>−60</td>
</tr>
<tr>
<td>Negative overall</td>
<td>0.85 ± 0.10</td>
<td>32 ± 14</td>
<td></td>
</tr>
<tr>
<td>1102: positive potentials (n = 8)</td>
<td>0.81 ± 0.28</td>
<td>40 ± 14</td>
<td>+58</td>
</tr>
</tbody>
</table>

Values are means ± SD.
potentials can be recorded over to the parasy Sylvian cortex (Fig. 1; cf. Duclaux et al. 1974).

The present cold potentials had longer latency and smaller amplitude than those of the first potentials evoked by electrical stimulation of the median nerve (22 ± 1 ms, 26 ± 3 μA), vibration of the distal palmar surface of the index finger (93 ± 2 ms, 29 ± 11 μA), or laser applied to the dorsum of the hand (136–140 ms, 54–71 μA) (Ohara et al. 2004). The variability of both latency and amplitude was much higher in the case of cold evoked potentials than that of any of the other potentials (Table 1).

These potentials may reflect many sources of variability, such as the uncertainty in identifying the onset of the temperature stimulus (Fig. 1), and the variance in that stimulus as 500 ms, the last temperature capable of influencing the EP, given conduction delays. In addition, the variability of these potentials may result from the staggered onset of activity and conduction velocities of Abeta/fast Adelta mechanoreceptors, and Adelta-specific cold receptors that may transduce and transmit the cold signal (Burton et al. 1972; Chatt and Kenshalo Sr. 1979; Duclaux and Kenshalo 1972). Finally, this slow potential could be the result of attention or novelty evoked by the cold stimulus, as in the case of the cutaneous laser stimulus (Legrain et al. 2002; Lenz et al. 2000).

In the previous scalp study, the averager was triggered by the signal that began cold water flow to the stimulator, which occurred before the present trigger from the change in temperature (Duclaux et al. 1974). The present EPs do not seem to be the result of input from the “high-threshold” cold receptors or deep cold receptors located around veins in the skin (Klement and Arndt 1992). Neither of these types of receptors would be activated in time to contribute to the cold EP since the temperature at 500 ms was 27°C, much too high to activate these receptors (Kenshalo and Duclaux 1977; Lamotte and Thalamhammer 1982). Whatever their origin, these delays are consistent with the slow dynamic phase of human thalamic cells to a cold stimulus (Lenz and Dougherty 1998).

The widespread distribution of cold EPs on either side of the Sylvian fissure may be explained by a generator described by a vector tangential to the surface of the brain, possibly in the insular or parietal cortex. This latter suggestion is consistent with the apparent phase reversal about the Sylvian fissure, on the assumption that thalamocortical volleys produce cortical surface positivity (Andersen et al. 1964; Vogel et al. 2003). The vector pointing across the Sylvian fissure at right angles to the surface positivity (Andersen et al. 1964; Vogel et al. 2003). The assumption that thalamocortical volleys produce cortical activity in response to nonpainful cold stimuli. An early response in the parietal operculum.

A vector pointing across the Sylvian fissure at right angles to the cortical surface positivity, consistent with a generator in the parietal operculum.

A wide range of imaging data suggests that parasympathetic structures show blood flow or blood oxygenation level–dependent activation in response to nonpainful cold stimuli. An early functional MRI study demonstrated that the insula was activated in one half of subjects, although localization within the insula was variable (Davis et al. 1998). The parietal operculum was not activated in that study, although a strong parietal opercular activation was observed in a positron emission tomographic study using a larger cold stimulus (Craig et al. 1996). In total, these results are consistent with the hypothesis that parasympathetic cortical structures display evoked responses to cold stimuli and thus implicate these structures in the sensation of cold.

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