Thermoreceptive innervation of human glabrous and hairy skin: a contact heat evoked potential analysis

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Abstract

The human palm has a lower heat detection threshold and a higher heat pain threshold than hairy skin. Neurophysiological studies of monkeys suggest that glabrous skin has fewer low threshold heat nociceptors (AMH type 2) than hairy skin. Accordingly, we used a temperature-controlled contact heat evoked potential (CHEP) stimulator to excite selectively heat receptors with C fibers or A\textsubscript{d}-innervated AMH type 2 receptors in humans. On the dorsal hand, 51\textdegree C stimulation produced painful pinprick sensations and 41\textdegree C stimuli evoked warmth. On the glabrous thenar, 41\textdegree C stimulation produced mild warmth and 51\textdegree C evoked strong but painless heat sensations. We used CHEP responses to estimate the conduction velocities (CV) of peripheral fibers mediating these sensations. On hairy skin, 41\textdegree C stimuli evoked an ultra-late potential (mean, SD; \textit{N} wave latency: 455 (118) ms) mediated by C fibers (CV by regression analysis: 1.28 m/s, \textit{N} = 15) whereas 51\textdegree C stimuli evoked a late potential (\textit{N} latency: 267(33) ms) mediated by A\textsubscript{d} afferents (CV by within-subject analysis: 12.9 m/s, \textit{N} = 6). In contrast, thenar responses to 41 and 51\textdegree C were mediated by C fibers (average \textit{N} wave latencies 485(100) and 433(73) ms, respectively; CVs 0.95–1.35 m/s by regression analysis, \textit{N} = 15; average CV = 1.7 (0.41) m/s calculated from distal glabrous and proximal hairy skin stimulation, \textit{N} = 6). The exploratory range of the human and monkey palm is enhanced by the abundance of low threshold, C-innervated heat receptors and the paucity of low threshold AMH type 2 heat nociceptors.

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1. Introduction

Psychophysical studies have shown that the glabrous skin of the human hand has a lower heat detection threshold than any cutaneous surface other than the lips (Stevens and Choo, 1998). Yet, glabrous hand skin has a much higher heat pain threshold than hairy skin (Taylor et al., 1993). Neurophysiological studies of the thermal innervation of monkey skin have provided a possible explanation for these differences by showing that glabrous skin, while richly innervated by heat-sensitive receptors with unmyelinated C fibers and high threshold nociceptors with finely myelinated A\textsubscript{d} fibers (AMH type I), is innervated sparsely, if at all, by lower threshold heat nociceptors (AMH type II) (Treede et al., 1995). In experiments relevant to this differential innervation hypothesis, Towell and colleagues (1996) examined the cerebral vertex potentials evoked by infrared laser stimulation of human hairy and glabrous (palm) skin.
These investigators evoked potentials mediated by both A\(\beta\) and C fibers from both glabrous and hairy skin. They could not, however, determine the type of A\(\beta\) fiber receptor that was excited by the laser stimulation. Based on reaction time experiments, they suggested that either A\(\beta\) or AMH type 1 fibers may have responded to laser stimulation of the palm (Towell et al., 1996).

In this paper, we present evidence that A\(\beta\) and C fibers innervating the human glabrous and hairy skin have different intensity dependencies and relative innervation densities. We used a newly developed contact heat evoked potential (CHEP) stimulator (Medoc Ltd, Ramat Yishai, Israel) to deliver rapidly-ramped contact heat stimuli that evoke late and ultra-late cerebral potentials reliably. CHEP stimulators have been developed and used by others to demonstrate the feasibility of this method in human neurophysiological studies (Arendt-Nielsen and Chen, 2003; Chen et al., 2001). An advantage of the device we used is that it delivers heat pulses with peak temperatures that are adjustable, monitored on-line and controlled by rapid feed-back, thus taking advantage of the differential heat thresholds of receptors innervated by C and A\(\beta\) fibers (Treede et al., 1995). To estimate the CVs of the fibers mediating these potentials, we measured evoked potential latencies among subjects with different arm lengths and within subjects following stimulation of proximal and distal arm locations; we also recorded the potentials evoked within subjects following glabrous and hairy skin stimulation of the hand and foot. Because glabrous skin occurs only at distal sites of extremities, we recruited a subject population with a wide range of arm lengths.

2. Methods

2.1. Subjects

Sixteen paid healthy volunteers (8 males and 8 females, ages 18–35 years) participated in this study. The data from one female subject was excluded due to a history of ongoing cervical pain. The local institutional review board of the Ann Arbor Veteran’s Affairs Medical Center approved the study protocol. Each subject signed a consent form after receiving a complete explanation about the purpose and design of the study.

2.2. Stimulator

We used a contact heat evoked potential stimulator (CHEPs, Medoc Ltd, Ramat Yishai, Israel), with a thermode that contacts a cutaneous area of 572.5 mm\(^2\). The thermode is comprised of a heating thermofoil (Minco Products, Inc., Minneapolis, MN) that is covered with a 25 \(\mu\)m layer of thermocative plastic (Kapton\(^*\), thermal conductivity at 23 °C of 0.1–0.35 W/m/K). Two thermocouples are embedded 10 \(\mu\)m within this conductive coating, which contacts the skin directly, thus providing an estimate of the skin temperature at the thermode surface. We confirmed the baseline temperature of the thermode surface and of the thermode-skin interface by measurements with an independent digital thermometer. Nonetheless, this estimate of skin temperature is necessarily an approximation because we did not insert intracutaneous thermocouples or thermistors in our subjects. Accordingly, the stimulus temperatures given throughout this report refer to the temperature of the thermofoil as applied to the skin surface. The thermofoil permitted a heating rate of up to 70 °C/s and the Peltier device allowed a cooling rate of 40 °C/s. Cooling began immediately following attainment of the target heat pulse temperature, which was set by the investigator using software provided by the manufacturer. The thermofoil-skin temperature is measured and software-controlled 150 times per second or just over 52 times during a 350 ms heat pulse (FWHM).

2.3. Procedure

Subjects sat in an armchair in a quiet room with an ambient temperature near 22 °C. We applied heat stimuli at two peak intensities, one potentially noxious (51 °C) and one innocuous, to five body sites: the right thenar eminence, the dorsum of the right hand, the proximal volar forearm, and the dorsum and sole of the foot. The innocuous temperature was 41 °C for all sites except the sole of the foot where the thick layer of the skin required a higher intensity stimulus (46–48 °C) to obtain sensations similar to those from the hand. The baseline temperature was 35 °C for all stimuli. The average time from onset to peak temperature was 190 ± 24 ms for 41 °C and 250 ± 8 ms for 51 °C.

Each stimulus block consisted of 20 constant-intensity stimuli applied to the same site at pseudorandom inter-stimulus intervals of approximately 15 s. The thermode remained at the same site during each block. We stimulated body sites in a pseudorandom order. To avoid sensitization and desensitization, low intensity stimuli preceded high intensity stimuli at the beginning of each block. To avoid expectation effects and to reduce the novelty effect on heat evoked potentials we applied several stimuli before beginning evoked potential recording. The subjects were given a 3–5 min break after each stimulation block.

The subjects rated the perception of each stimulus 3 s after stimulus onset. The ratings were based on a 0–10 level numerical ranking scale. The extremes of the scale were ‘no sensation’ at 0 and ‘unbearable burning sensation’ at 10. A level of 4 was the threshold for a pinprick-like pain sensation.

2.4. Contact heat evoked potential recording

Contact heat evoked potentials (CHEPs) were recorded from six midline electrodes (Fz, FCz, Cz, CPz, Pz, POz) using an electrode cap that contains 59 electrode positions according to the 10%-system, an extended montage of the standard 10–20 system. Here, we report only data recorded from the Cz (vertex) position. Linked earlobe electrodes served as reference. The electroencephalogram (EEG) was recorded within a 0.15 and 100 Hz bandpass and digitized at a sampling rate of 500 Hz. For artifact control, we monitored the electrooculogram (EOG) from supra- and infraorbital electrodes. The impedance from all electrodes was below 5 k\(\Omega\). EEG data were stored on disk and analyzed off-line (Scan 4.2, Compumedics USA, El Paso, TX, USA). Each recording epoch of 2600 ms included a period of 200 ms baseline before stimulus onset, which was initiated by a TTL pulse at the beginning of the temperature increase.
2.5. Data analysis

Peri-stimulus epochs contaminated by ocular artifacts were discarded and not included in signal averaging. We averaged the remaining sweeps separately for stimulus intensity and stimulus site. Within each individual’s average waveform, we identified the peak latency and amplitude of the major negative and subsequent positive peaks of the evoked potentials.

To estimate the conduction velocity (CV) of peripheral nerve fibers mediating evoked potentials, we used a tape measure on the fully abducted arm to estimate the distance from the middle of the thenar eminence and the corresponding site on the dorsum of the hand to the C7 vertebral spinous process (straight arm abducted 90° from the trunk); we also measured the distance between the sites of thenar and proximal forearm stimulation in each subject. Because glabrous skin is located distally only, we used a regression analysis to estimate the conduction velocity of peripheral nerve fibers from latency differences in the potentials evoked from all subjects. We plotted the latencies of negative and positive peaks in milliseconds as a function of arm length in millimeters and used linear regression analysis. The regression coefficients define the slope of the regression curve and its intercept at the ordinate; the reciprocal of the slope parameter is an estimate of the CV in meters per second. This method of analysis obviates the need for applying corrections for differences between nerve and arm length over long distances (Kakigi and Shibasaki, 1991) because a single estimate is made over a small range of different conduction distances (210 mm). The same analysis was applied to data obtained from a subpopulation of our subjects (N = 11) from whom both late and ultra-late potentials could be evoked from hairy skin. We performed a repeated measures analysis of variance (ANOVA) to evaluate the effect of stimulus site (hairy versus glabrous skin) and intensity (low versus high) on intensity ratings, and on the latency and amplitude of evoked potential components. Sources of any significant main and interaction effects were explored using two-tailed paired t-tests.

In a subpopulation of 6 subjects, we were able to evoke potentials following 41 °C stimulation of the proximal forearm and following 51 °C stimulation of the dorsal hand and proximal forearm. In these subjects, we performed conduction velocity estimates directly from the intra-individual differences in latency and conduction distance.

Because of the variance introduced by individual differences in peripheral CV and central delays, we wished to confirm the validity of the inter-subject CV estimates and the intra-subject estimates obtained from the small sub-samples of subjects. Accordingly, we measured the difference between the latency of the late potential evoked by noxious stimulation of hairy skin and the ultra-late potential evoked by high or low intensity stimulation of glabrous skin in each subject. Assuming negligible differences in intra-individual fiber conduction velocities and central conduction delays, this analysis allows an estimate of the changes in the latency difference that would be expected from conduction velocity differences between peripheral fiber populations. Thus, if \( \Delta_{\text{latency}} \) = the increased latency difference (ms) between the earliest (late) and latest (ultra-late) evoked potentials in two individuals with different arm lengths, \( m_1 > m_2 \), then

\[
\Delta_{\text{latency}} = (m_1 - m_2)/(1/CV_{a} - 1/CV_{l})
\]

where \( CV_{a} = \) conduction velocity (m/s) of fibers mediating the latest (ultra-late) potential and \( CV_{l} = \) conduction velocity of fibers mediating the earlier (late) potential. Thus, for fixed arm length differences, the latency difference is determined primarily by the relative conduction velocities of the peripheral fibers. Since the latency difference is positively related to arm length, the latency difference observed across the range of arm lengths should be within the range of values computed in the above equation from CV estimates obtained within and across individuals. We will present the comparison between hand and foot data only descriptively, because it involves an additional difference in spinal conduction time.

3. Results

3.1. Intensity ratings

Stimulation of glabrous skin at the thenar produced sensations of mild and strong painless warmth at peak temperatures of 41 and 51 °C, respectively. In contrast, 51 °C stimulation of the hairy skin of the dorsum of the hand always produced a moderately painful pinprick-like sensation and a warm sensation only following stimuli at 41 °C. The mean intensity ratings for the two peak temperatures at either skin site are represented in Fig. 1. Two-way repeated measures ANOVA with site (glabrous and hairy) and intensity (41 and 51 °C) as variables yielded significant intensity (\( F_{1,14} = 125.7; P < 0.001 \)) and site (\( F_{1,14} = 44.7; P < 0.001 \)) main effects and a significant intensity-by-site interaction (\( F_{1,14} = 20.2; P = 0.001 \)). This result is due to the greater intensity rating following 51 °C (\( t = 11.2; P < 0.001 \)), a greater intensity rating at hairy than glabrous skin (\( t = 6.7; P < 0.001 \)), and a greater intensity difference at hairy than at glabrous skin (\( t = 4.5; P = 0.001 \)).

3.2. Contact heat evoked potentials (CHEP)

Thenar stimulation at peak pulse temperatures of 41 and 51 °C evoked well-defined potentials in all 15 participants.
Fig. 2a shows the waveforms evoked in five representative subjects following stimulation of the glabrous skin at 41 °C. Subjects are ordered from top to bottom row according to increasing arm lengths indicated at the left of the tracings. Broad negative-to-positive ultra-late components are discernible between 400 and 900 ms poststimulus; these responses shift to longer latencies with increasing arm length. Fig. 2b shows the waveforms evoked in the same subjects following the 51 °C stimulus applied to the hairy skin of the hand dorsum. These shorter duration negative-to-positive late components appear between 250 and 500 ms and vary little with arm length.

Table 1 shows the average latency and amplitude values of both negative and positive components following 41 and 51 °C stimuli applied to glabrous and hairy skin sites of the hand. Repeated-measures ANOVA of the peak-to-peak amplitudes revealed a significant site-by-intensity interaction ($F_{1,10} = 11.1; P = 0.008$) and no main effects of either site ($F_{1,10} = 1.9; P = 0.2$) or intensity ($F_{1,10} = 0.5; P = 0.5$). This result was due to the higher effects of intensity when stimulating hairy skin ($t = 2.9; P = 0.016$). The latency of the negative wave showed significant main effects for both site ($F_{1,10} = 28.9; P < 0.001$) and intensity ($F_{1,10} = 22.4; P < 0.001$) and significant site-by-intensity interactions ($F_{1,10} = 38.1; P < 0.001$). This result is because high intensity stimuli caused shorter evoked potential latencies than low intensity stimuli ($t = 4.73; P = 0.001$), an effect which was greater on hairy skin ($t = 6.17; P < 0.001$). The generally shorter latencies following hairy skin stimulation ($t = 5.37, P < 0.001$) explain the significant main effect of site. Notably, entering arm length as a covariate in the ANOVA eliminated all site and intensity main and interaction effects, and revealed the expected significant main effect of arm length on latency ($F_{1,9} = 11.1; P = 0.009$) that also showed an interaction with site ($F_{1,9} = 5.6; P = 0.04$). This result suggests that the variance of the ultra-late N-wave latency is largely due to a slower peripheral conduction time following low compared to high intensity stimulation of glabrous compared to hairy skin. The P-wave latency was more variable than the N-wave latency, but yielded a similar result.

Thus far summarized, the results indicate higher pain sensitivity of hairy compared to glabrous skin; warm sensitivity showed little difference between these sites. Consistent with the subjective ratings, CHEPs have greater amplitudes and shorter latencies when evoked from hairy
compared to glabrous skin, an effect which was greater for high intensity stimuli. Next, we address the hypothesis that the latency difference is due to activities originating from different peripheral fiber spectra.

3.3. Conduction velocity estimates

Figure 3 shows the data points and linear regression curves with upper and lower confidence levels (95%) for latencies of the first major negative wave following low and high intensity stimuli applied to the glabrous (top) and hairy (bottom) skin sites of the hand plotted as a function of arm length. Low intensity stimulation of hairy skin failed to evoke any responses in 4 subjects; therefore, we show data from only 11 subjects for this condition. CVs derived from the slope of the regression curves yield 0.95 and 1.35 m/s for glabrous skin following 41 and 51 °C stimuli, respectively, and 1.28 m/s for hairy skin following 41 °C stimuli. In contrast, 51 °C stimulation of hairy skin evokes potentials with significantly shorter latencies and a flatter regression curve. The CV calculated from the slope of the regression following high intensity stimulation of hairy skin is 3.91 m/s. However, these estimates of CV are compromised by several variables, including arm length measurements and possible inter-subject differences in the CV of myelinated and unmyelinated fibers. The greatest error is in estimating the CV of fibers mediating the shorter latency responses because the effect of small measurement errors is magnified. Moreover, the statistical significance level for regressions obtained from the hairy skin is smaller for both high intensity ($r^2=0.29; P=0.03$) and low intensity stimulation ($r^2=0.23; P=0.13$) than those obtained for both intensities from the glabrous skin (41 °C: $r^2=0.61; P=0.001$; 51 °C: $r^2=0.52; P=0.002$). Accordingly, we obtained additional estimates of the CV of fibers mediating both the late and ultra-late potentials evoked from hairy skin within a subgroup of our subjects as presented below.

Most high intensity stimuli applied to hairy skin evoked only late, but no ultra-late responses; low intensity stimuli often failed to evoke any responses. However, we were able to obtain ultra-late responses after stimulating the proximal volar forearm with 41 °C in 6 subjects, which allowed a direct within-subject comparison with ultra-late responses following a 41 °C stimulus to the thenar. Because the 51 °C stimuli evoked late components following stimulation of both the dorsal hand and the proximal forearm, we could estimate and compare directly the CV mediating late and ultra-late responses in these individuals. The results are presented in Table 2A and B and sample responses from three of these subjects are shown in Fig. 4. The average conduction velocity is 1.7 ± 0.4 m/s for fibers mediating the ultra-late potential in these 6 subjects and 12.9 ± 7.5 m/s for fibers mediating the late potential. Note that the estimated average CV derived from the ultra-late potential applies only to the applied stimulation of 41 °C and is based on stimuli applied to different skin types (glabrous and hairy). Given the relatively short distance used for all of these estimates, they are not affected significantly when corrected for estimations of nerve length in relation to arm length (Kakigi and Shibasaki, 1991).

To confirm further the CV estimates obtained both within and across subjects, we computed the latency difference between the late and ultra-late negative and positive potentials evoked from hairy and glabrous skin for each individual. This within-subject latency difference will
increase with arm length according to the equation presented in Section 2. This measurement reduces the variance introduced by inter-subject differences in peripheral conduction velocities and central conduction times. As shown in Fig. 5, negative (filled squares) and positive (open triangles) ultra-late components following all glabrous heat stimuli had increasing latency differences relative to the late components following heat stimulation as arm length increased across subjects. The intercept of the regression line predicts a latency difference of approximately 100 ms for an arm length of 600 mm, which is close to the value obtained from the shortest subject in our sample (130 ms over 640 mm). The direct estimate of the average CV of fibers mediating the late and ultra-late potentials obtained from the subgroup of six subjects (12.9 and 1.7 m/s, respectively) predicts an increase in the latency difference between these potentials of 107 ms over the maximum arm length difference of 210 mm (850–640 mm) (see equation in Section 2). The estimates obtained from the regression analysis of latencies on arm length across 15 subjects predict latency differences ranging from 139 to 204 ms over this same conduction distance. All of these predicted latency differences are within the 100–300 ms range of the latency difference increases obtained from the regression across the 210 mm range of arm lengths as shown in Fig. 5. Thus, the within-subject late and ultra-late latency differences are consistent with the CVs estimated by the regression analysis of group differences in ultra-late latency and by a sub-sample of direct within-subject measurements. The discrepancy between the within-subject and across-subject estimates for the CV mediating the late response is attributable to the additional variance introduced by inter-subject differences in conduction distance and both peripheral and central conduction times.

The results provide strong evidence that: (1) there is a difference in the abundance of slowly and rapidly conducting thermo-nociceptive afferents innervating the glabrous and hairy skin of the human hand, and (2) that the receptors innervated by these different fiber spectra have different thermal sensitivities.
To evaluate further whether these functional differences also apply to the foot, we applied similar heat stimuli to the glabrous skin of the sole and the hairy skin of the dorsum of the foot. We found that in some individuals it was difficult to get responses from the glabrous skin of the foot probably because of skin thickness. However, when responses appeared, they were markedly delayed compared to the responses from the dorsal hairy skin. Thus, stimulation of the glabrous sole at either temperature (46–51 °C) evoked an ultra-late heat potential in six subjects, which was associated with a sensation of warmth. The latency difference between the potential evoked by stimulation of glabrous skin of the sole and the hand ranged from 600–900 ms. In contrast, stimulation of the dorsum of the foot with 51 °C pulses evoked late potentials with much shorter latencies (ranging between 120–150 ms to the first negative peak) associated with a strong, sharp pain.

4. Discussion

Our data show that (1) the ultra-late potentials evoked from glabrous skin by 41 and 51 °C stimuli and from hairy skin by 41 °C stimuli are mediated by unmyelinated (C) fibers and (2), the late potential evoked from hairy skin by 51 °C stimuli is mediated by finely myelinated Aδ fibers. These interpretations are consistent with the late potential being associated with pinprick sensations and the ultra-late potential with mild to strong warmth. The findings and conclusions are consistent with those obtained by recordings from fibers innervating monkey skin (Treede et al., 1995) and with human psychophysical experiments (Stevens and Choo, 1998; Taylor et al., 1993).

Zaslansky and colleagues (1996) have presented evidence that the pain-related laser-evoked late potential contains cognitive components. It is unlikely that our results are confounded by P300-like potentials associated with attention and cognition because of the strong positive relationship between evoked potential latency and arm length (Lorenz and Garcia-Larrea, 2003). Furthermore, cerebral potentials mediated by C and Aδ fibers are physiologically distinct from P300 cognitive potentials (Towell and Boyd, 1993).

4.1. Peripheral and central timing

The average latency of the C-fiber mediated potentials we recorded is shorter than that obtained by brief laser stimulation of very small skin areas (Bragard et al., 1996; Kakigi et al., 2003; Opsommer et al., 1999; Tran et al., 2001, 2002). In addition, the average latencies for the Aδ-mediated contact heat potentials are slightly longer than those reported for the Aδ-mediated potential evoked by brief laser stimulation of a larger skin area (Bromm and Lorenz, 1998; Kakigi and Shibasaki, 1991; Kakigi et al., 2000; Lorenz and Garcia-Larrea, 2003).

The different results we obtained are probably due to several critical variables, including the location, temperature, duration, and surface area of the stimuli. These variables affect the composition, dispersion, and magnitude of the afferent volley, which affects central temporal and spatial summation and, therefore, the timing of activity ascending to the cerebral cortex. We applied temperature-controlled pulses that are approximately 10 to 300 times longer over a surface area 30 to 3000 times greater than those typically used in laser evoked potential studies. Furthermore, we applied stimuli that were physiologically selective because the lowest intensity exceeded the threshold for heat receptors innervated by C fibers but was...
below the threshold for all receptors innervated by Aδ fibers; the highest intensity was below the threshold for type 1 AMH nociceptors. Brief laser stimulation of very small skin areas must excite many fewer C fiber-innervated receptors than our contact heat stimuli, which may explain the shorter latencies of our C fiber-mediated potentials. As estimated from the within-subject studies, the CV of the fibers mediating the ultra-late potential is 1.7 m/s (Table 1A), which slightly exceeds some previously reported values (see, for example Kakigi et al., 2003; Tran et al., 2001, 2002), but is less than the estimates of others (Magerl et al., 1999). The CV of these fibers ranged from 0.95 to 1.35 as estimated by the regression method from all subject participants and is within the lower ranges reported by others (Kakigi et al., 2003; Tran et al., 2001, 2002).

To validate our results, the average peripheral conduction time should be less than the average evoked potential latency. The best estimate is provided by using the average CV obtained from our within-subject analysis because small measurement errors may give individual CV estimates that yield negative values for individual central conduction time (for example, subjects 4 and 6, Table 2A). Using the average CV of 1.7 m/s, the average peripheral conduction time is 434 ms over the average arm length of 737 mm (Table 1) for 15 subjects. The average N wave latency for 41 °C stimulation of glabrous skin is 485 ms (Table 1), leaving 51 ms for the estimated average central conduction time. The average conduction velocity of heat-responsive primate spinothalamic tract neurons ranges from 17 to 51.6 m/s (Ferrington et al., 1987; Willis et al., 1974; Zhang et al., 2000a,b), so a 51 ms conduction time is adequate for the central conduction time obtained following laser stimulation (Bragard et al., 1996; Bromm and Treede, 1988, 1991; Opsommer et al., 1999). These observations were supported by neurophysiological evidence of A fiber inhibition of C-mediated spinal responses (Chung et al., 1984a,b) and led to the development of special techniques to avoid the excitation of receptors with Aδ afferents by restricting the area of skin stimulation (Bragard et al., 1996; Kakigi et al., 2003; Opsommer et al., 1999; Tran et al., 2001).

Special stimulating, recording, and selective averaging methods have also been used to detect the C fiber-mediated ultra-late responses (Arendt-Nielsen, 1990; Bragard et al., 1996; Towell et al., 1996). By selecting a relatively large stimulus area, an intensity below the threshold for exciting Aδ afferents, and by focusing on a skin area richly supplied with C-innervated heat receptors, other investigators have evoked C fiber-mediated ultra-late potentials selectively with laser stimulation (Cruccu et al., 2003; Iannetti et al., 2003; Magerl et al., 1999; Valeriani et al., 2002a,b). Other CHEP methods have been used recently to evoke cerebral potentials mediated by Aδ afferents, but the selective excitation of C fibers could not be established (Arendt-Nielsen and Chen, 2003; Chen et al., 2001; Harkins et al., 2000; Itskovich et al., 2000; Valeriani et al., 2002). Compared to most laser stimulation techniques, the advantages of the CHEP method include the control of peak temperature and the possibility of stimulating more receptors with a relatively long duration pulse over a much larger surface area. The Aδ-mediated laser evoked potential is abnormal in early diabetic polyneuropathy (Agostino et al., 2000a,b), so the ability to assess C fiber function by both laser and contact heat may facilitate the detection of small fiber polyneuropathies (Krarrup, 2003).

4.3. Comparison of hairy and glabrous skin

Towell and colleagues (1996) recorded cerebral potentials mediated by Aδ fibers following both painful and painless laser stimulation of the glabrous skin of the palm. The most intense contact heat stimulus we applied to glabrous skin (51 °C) failed to evoke an Aδ-mediated potential of shorter latencies.
response. Because 51 °C is below the average threshold of monkey AMH type 1 receptors but above that of AMH type 2 receptors, the combined evidence supports the interpretation that the human palm has few, if any, AMH type 2 receptors. The possibility that AMH type 1 receptors in human glabrous skin may be excited by innocuous infrared laser stimulation is consistent with estimates of receptor depth and laser heat distribution in the skin (Haimi-Cohen et al., 1983; Tillman et al., 1995).

Our findings support the hypothesis of Treede and colleagues (1995) about the differential innervation of monkey hairy and glabrous skin and extend the hypothesis to include the human hand. The combined neurophysiological and psychophysical data (Gescheider et al., 1994; Greenspan et al., 1993; Stevens and Choo, 1998; Schlereth et al., 2001; Taylor et al., 1993), suggest that the glabrous surface of the primate hand has a wide range of thermal and mechanical sensitivity which, together with the relative paucity of low threshold heat nociceptors, enhances its function as an exploratory surface.

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