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Latency to Detection of First Pain

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The latency to detection of heat stimuli applied to the distal forearm and thenar eminence was measured in 3 subjects in order to determine whether short latency responses correlated with perception of first pain. Only one temperature was used in a given run and stimuli ranged from 39 to 51 °C. In addition, subjects were interviewed at the end of each run regarding the quality of sensations experienced. In one series of experiments the quality of the first sensation evoked by each stimulus rather than latency was recorded. The median response latency decreased exponentially from 1100 ms to 400 ms for the distal arm and 1100 ms to 700 ms for the hand. The higher temperatures elicited a double pain sensation on the arm, but not on the glabrous hand. Warmth was always the first sensation felt on the hand. It is concluded that short latencies (less than 450 ms) reliably denote the presence of first pain, and that at least some portion of the primary afferents that signal first pain must have conduction velocities greater than 6 m/s.

INTRODUCTION

The time (response latency) that a subject takes to indicate detection of a stimulus customarily decreases exponentially as a function of stimulus intensity[17]. In the case of heat stimuli applied to the skin of the distal extremity the sensation changes from a feeling of warmth to one of pain as the stimulus intensity increases[23]. The pain evoked may consist of two distinct sensations, namely, first pain and second pain[5,12,21,22,26–28]. First pain is of short latency, and short duration, and is signalled by activity in myelinated primary afferents[22,27]. Second pain is of longer latency, and longer duration, has a quality of burning, and is served by slowly conducting unmyelinated afferents[1–3,5,9,13,14,19,22,23,30]. Afferents that signal warmth also appear to have slow conduction velocities, either in the C-fiber or slow A-δ fiber range[4,10,16,18,23,29] and therefore probably conduct more slowly than afferents that mediate first pain. Conduction time is an important factor in determining the latency of detecting a heat stimulus delivered to the more distal regions of the limb. It follows that in those instances where heat stimuli elicit both sensations of first pain and warmth, that the former might be perceived sooner than the latter and therefore detection latency might provide indirect but objective information about the quality of sensation. That is, fast latencies of detection would denote the presence of first pain. The latency measurement technique could therefore be used to estimate first pain threshold in man, and might also be used to ascertain the presence of pain in non-human primates.

Measurements of response latency to noxious heat stimuli have been made in the past, but it has been difficult to measure latency as a function of stimulus intensity for several reasons: the latency to touch is less than the latency to warmth or heat pain and thus it is necessary that skin contact not be initiated at the time of heat stimulation. Secondly, the rise time from the base to the desired temperature needs to be rapid. A third point is that it is desirable to regulate temperature, rather than the rate of temperature transfer, as sensory magnitude is more dependent on the skin temperature, than on the speed (within certain limits) with which the temperature is reached[15]. Each of these technical points has been satisfactorily solved in recent years with the development of a laser thermal stimulator, which allows

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constant temperature stimuli to be applied to the skin from a non-contact source, with rapid rise times (< 250 ms for each temperature) to the desired temperature[25].

The results reported in this study corroborate the supposition that myelinated nociceptive afferents signal first pain. Moreover it is suggested that short latencies of response (< 450 ms) denote the presence of first pain. It is thus possible to infer the presence of pain by the measurement of response latency, independent of verbal ratings.

METHODS

Heat stimuli were applied to the skin with the use of a laser thermal stimulator[25]. Step increases in skin temperature were applied to a 7.5 mm diameter spot without mechanical contact with the skin. Rise times to the desired temperature were 200–250 ms, substantially faster than those of most other thermal stimulators, such as the Hardy-Wolff-Goodell dolorimeter[15].

One female and two male right-handed human subjects between the ages of 22 and 35 years were studied. Each run consisted of 40 presentations of the same stimulus temperature, each stimulus being 2 s in duration. The stimuli used in the different runs ranged from 39 to 51 °C, and were superimposed on a base temperature maintained at 38 °C between stimuli. The interstimulus interval varied within a given run, and ranged from 15 to 31 s with a mean of 23 s. Eight loci were stimulated in rotating sequence. The thenar eminence was stimulated in half of the runs, and the volar forearm in the other half. Typically two runs were administered per day, one run on the forearm and the other run on the thenar eminence. The order of the runs was alternated from day to day. The mean interval between stimuli delivered to the same locus was 198 s. A warning buzzer signaled the beginning of each trial, which the subject initiated by pressing down and holding a key in this position. The subjects were instructed to release the key as soon as an increase in temperature was detected regardless of whether pain or warmth was the first sensation. The stimulus was given on a random basis in one of 5 contiguous intervals, each of 2 s duration, beginning 2 s after the warning buzzer. The distribution of stimulus intervals was closely monitored to ensure that for each temperature each interval was used approximately the same number of times. Response latency was defined as the interval between stimulus onset and key release. A LINC computer was used to control stimulus timing, set and monitor stimulus temperature, and record response latencies. Subjects were asked at the end of each run to describe what sensations were felt, particularly with regard to what sensation was felt first. Trials in which the key was not released during the stimulus interval were considered either anticipations (key up before stimulus) or misses (key up after stimulus) and were excluded from the analysis. The subjects were informed by panel lights and tones delivered via earphones after each trial whether the response was correct, a miss, or an anticipation.

In pilot experiments an attempt was made to obtain verbal reports of the quality of the first evoked sensation at the same time latencies were measured. This procedure proved to affect adversely the reaction time and was therefore abandoned. In lieu of this a series of experiments was conducted in one of the subjects, in which instead of measuring response latency, the subject was asked to indicate the quality of first sensation evoked by the first stimulus. Stimulus conditions were the same as in the latency experiment. Each run was administered on a separate day, and temperatures of 41, 43, 45 and 46 °C were delivered to the volar forearm. Each temperature was presented 40 times for a total of 160 trials.

RESULTS

The 3 subjects in total received 7560 stimuli. Of the responses to these, 4 % were misses and 7 % were anticipations. Over 50 % of the misses and anticipations occurred at temperatures of 39 and 40 °C. The stimulus of 39 °C was near the detection threshold and the latencies obtained were not considered valid and therefore will not be considered further.

The data for the 3 subjects was similar and therefore combined. The detection latencies decreased as a function of stimulus temperature. The results are shown in Fig. 1 separately for the stimuli presented to the volar forearm, and thenar eminence. The latencies for the thenar eminence and volar forearm were similar up to 45 °C. Above 45 °C the volar forearm latencies were shorter than the thenar eminence latencies. The median latencies reached a plateau near 400 ms for the volar forearm, and a plateau near 700 ms for the thenar eminence.

In addition to a difference in latency for the two types of skin, there was also a difference in the quality of sensation. For the volar forearm, each of the subjects reported that the lower stimulus temperatures evoked warmth as the first sensation, while at the higher temperatures a sequence of first and second pain was reported in which first pain was clearly felt prior to any other sensation. The first pain sensation was described as being brief and pricking in quality, while second pain was described as having a burning quality. There was no first–second pain sequence for the thenar eminence and warmth was the first sensation experienced regardless of temperature. Subjects reported that when pain was evoked by stimuli presented to the thenar eminence, it followed the sensation of warmth, and was comparable in quality to the second pain felt on the volar forearm.

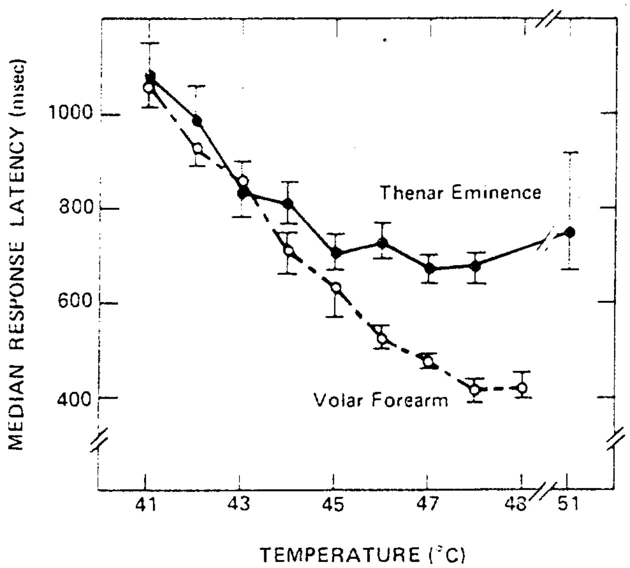

Fig. 1. The median response latency for 3 subjects combined is plotted along with 95% confidence limits as a function of stimulus temperature. Latency decreased with increases in temperature to a plateau of 700 ms in the case of stimuli presented to the thenar eminence of the hand, and 400 ms for stimuli presented to the distal volar forearm. The 'n' (misses, anticipations deleted) for each temperature is given for the thenar and forearm respectively: 40 °C-258, 191; 41 °C, 333, 282; 42 °C, 314, 287; 43 °C, 680, 707; 44 °C, 405, 481; 45 °C, 418, 576; 46 °C, 343, 543; 47 °C, 156, 114; 48 °C, 0, 80; 51 °C, 37, 0.

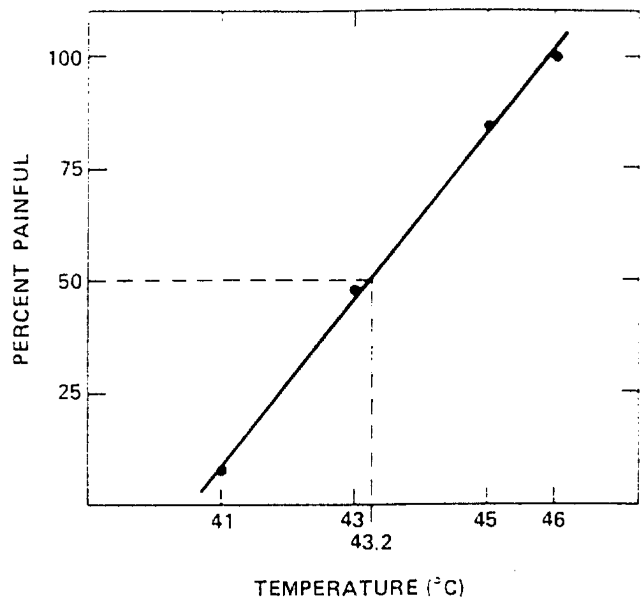

Fig. 2. The percent of trials in which a double pain sequence occurred, and in which first pain (not warmth) was the first sensation that denoted perception of a temperature increase. The stimuli were presented to the distal volar forearm using the same procedures as in the latency experiment, except that verbal descriptions of the evoked sensation rather than latency were measured.

The relation between short latencies and first pain on the volar forearm

Though detection latencies and subjective reports were not obtained concurrently, each subject reported that at the higher temperatures a first pain sensation triggered the detection responses for the volar forearm. To corroborate this impression, a separate experiment was conducted in one subject, which consisted of having the subject report the first sensation evoked by each stimulus temperature.

The percentage called painful increased linearly as a function of stimulus intensities from 41 to 46 °C, as shown in Fig. 2. The pain threshold (the '50% called first pain' point), as determined by linear interpolation, was 43.2 °C. A histogram showing the distribution of response latencies at each temperature for the same subject is shown in Fig. 3. By comparing Figs. 2 and 3 it can be seen that the number of fast latency responses as a function of stimulus intensity corresponded closely to the percentage labeled first pain. At 43 °C, for example, nearly one-half of the latencies were fast, which correlates well with the 43.2 °C first pain threshold.

Further corroboration came from the observation that when intermediate intensity temperatures were

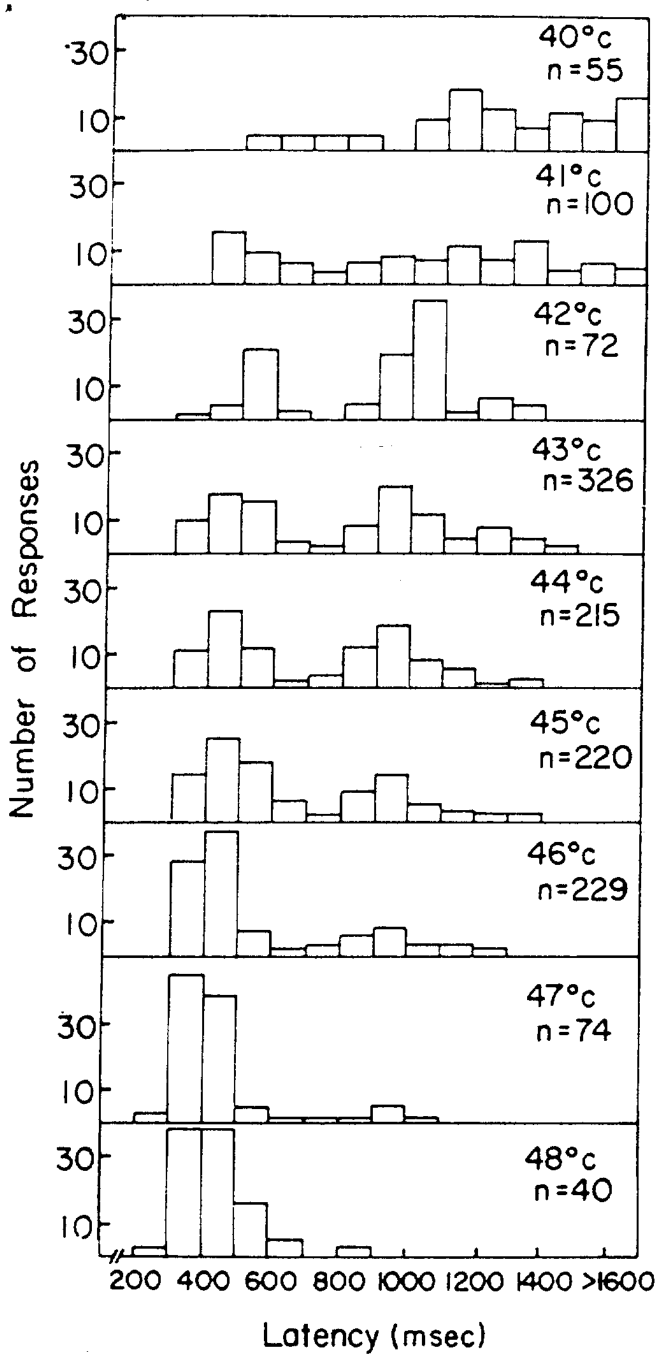

Fig. 3. The distribution of response latencies for each temperature for stimuli delivered to tne volar forearm. The subject is the same as the one for whom data is shown in Fig. 2.

presented to the volar forearm, certain loci were associated with long latency responses, while other loci were associated with short latency responses. The subjects were interviewed with regard to the sensations evoked by stimulation of long latency loci and short latency loci. The first sensation felt at the long latency locus was in each instance that of warmth, while the first sensation felt at the short latency locus was that of first pain.

Conduction velocities of primary afferents that signal first pain and warmth

An estimate of the slowest possible conduction velocities of primary afferents that signal first pain may be made if certain assumptions are allowed. To estimate the sum total of time necessary for central sensory processing, the decision making plus motor execution times were measured in one subject for responses to suprathreshold auditory stimuli. Auditory stimuli were chosen because primary afferent conduction time is negligible. Latencies were measured in the same way as with the thermal stimuli. The tenth percentile (point at which 10% of the latencies were faster and 90% were slower) was near 0.19 s. The tenth percentile of the thermal latencies at 47 °C for the volar forearm for the same subject (the subject with the fastest volar forearm latencies) was 0.33 s. The conduction distance from the area stimulated to the spinal cord was 0.78 m in this subject. If receptor utilization time, rise time, and conduction time in the cervical spinal cord are ignored, then primary afferents that signal first pain must have a conduction velocity of at least 0.78 m/(0.33 — 0.19) s, or 6 m/s.

A similar analysis may be used to estimate the conduction velocity of afferents arising from the thenar region that signal warmth. As indicated above, warmth was the first sensation noted regardless of stimulus intensity for the thenar area. The tenth percentile of latencies for the subject with the fastest thenar latencies at 46 °C was 0.48 s. The conduction distance to the spinal cord in this subject was 0.68 m. Assuming a similar latency for auditory stimuli, the conduction time of the fastest primary afferents that mediate warmth sensation in humans must be at least 0.68 m/(0.48 — 0.19) s, or 2.3 m/s.

DISCUSSION

It has long been suspected that first pain is signaled by myelinated nociceptive afferents[5,21,22]. The latency data obtained in this study affirm this concept, and suggest that at least some portion of these fibers must have a conduction velocity greater than 6 m/s.

Although many investigators have recorded responses to heat from myelinated nociceptive afferents with conduction velocities greater than 6 m/s, not all of these fibers would be candidates to signal first pain. We, and others, identified a class of nociceptive A-fibers in monkey that have an initial high thermal threshold[7]. The receptor utilization time, i.e. the time necessary for the receptor to be activated by natural stimuli, was found to be greater than 500 ms, and thus these fibers cannot be candidates for participation in behavioral responses that denote perception within 400 ms. The receptor utilization time was estimated as the difference between the latency of the response to natural stimuli minus the latency of response to electrical stimuli applied to the receptive field. A sequence of first and second pain is not felt on the face[22], probably because the contribution of primary afferent conduction time to the total latency of perception is too small for activity in unmyelinated and myelinated nociceptive fibers to elicit temporally distinct sensations. Dubner et al.[11] recorded from monkey face heat-sensitive A-δ nociceptive fibers that might be capable of signaling first pain. We recently recorded from several A-fiber nociceptive afferents with conduction velocities greater than 6 m/s that innervated hairy skin of the monkey arm (Meyer and Campbell, unpublished observations) that have receptor utilization times less than 50 ms, and would be candidates to signal first pain.

First pain was not evoked by stimulation of the glabrous skin of the hand. This is probably a matter of threshold, as there is evidence that first pain can be evoked with stimuli above 51 °C applied to the thenar eminence (R.H. LaMotte and J. G. Thalhammer, unpublished observations). Because warmth was the first sensation evoked on the thenar skin it was possible to estimate the conduction velocity of warm fibers. It was determined from latency data in this study that warm fibers must exist that have a conduction velocity of 2.3 m/s or more. Sumino et al.[29] studied warm fibers on the monkey face, and the mean conduction velocity was 3.3 ± 1.9 m/s. Darian-Smith et al.[10] found that the conduction velocity of warm fibers in the monkey hand ranged from 0.6 to 2.4 m/s, with a mean of 1.2 m/s. LaMotte et al.[20] found that the mean conduction velocity of warm fibers in the monkey hand was 1.5 ± 0.5 m/s. The conduction velocities of two warm fibers in humans have been estimated to be 0.5 and 0.8 m/s[13].

From these considerations there is clearly a tenable neurophysiological basis by which the detection of warmth and first pain may be distinguished by the measure of response latency. The sensation associated with a long latency response may be either that of warmth or pain, but a latency of response to a heat stimulus applied to the distal extremity between 300 and 450 ms suggests that first pain has been detected.

This study, then, reveals a means by which the presence of first pain may be ascertained without asking the subject what he feels. The response latency measure might therefore be used to establish an anchor for measures of pain sensitivity by the method of signal detection[3], or an anchor for subjective scales of the magnitude of pain[23]. Finally, because the latency measure is feasible in animals, this technique may be used to measure the threshold to first pain in non-human primates.

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