Stimulus–response relations in high-threshold mechanothermal fibers innervating primate glabrous skin

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In a previous paper I described some of the functional properties of 536 high-threshold primary afferents (345 A δ and 191 C fibers) which innervated the glabrous skin of the monkey hand, namely their responses to intense mechanical and thermal stimuli. A major finding of that study was that there exist within the A δ and C groups of primary afferents large sets of fibers which respond to both mechanical and thermal stimuli of high intensity. In what follows I present the results of quantitative studies performed on a sample of such A δ and C mechanothermal fibers by observing their responses to heat and cold stimuli graded in intensity.

A special servo-controlled contact thermostimulator was used in the present study. The details of its design, construction and performance have been described elsewhere. This stimulator allows the active regulation of the temperature of a region of the skin approximately 1 cm in diameter. Heating and cooling pulses can be generated successively; they are free of any associated mechanical stimulation of the skin. Stimulus temperatures are controlled by a feedback system with a thermocouple at the thermode–skin interface; they are largely independent of varying thermal loads imposed by the underlying tissue. The stimulus used was a near-rectangular displacement of the temperature at the thermode–skin junction (a temperature pulse, Fig. 1). For a stimulus temperature change of 10 °C the response time (time to reach (1−1/e) amplitude), including transport delays, was 0.25 sec. The baseline temperature (T-base) from which the thermal pulses were delivered was set at 39 °C for heat and at 30 °C for cold studies. No stimulus sequence was begun until the skin temperature had been fixed at the selected T-base level for a period of 10 min. Temperature pulses, usually of 3 sec duration, were then applied to the most sensitive site of the receptive field of a fiber under study; the temperature was actively returned to the appropriate baseline level during the interstimulus interval which was set at 60 sec. Stimuli were applied in ascending series only. The intensity of the temperature pulses delivered was increased by steps of 1 °C (or 2 °C in a few experiments), up to 14 and 15 °C heat and cold pulses respectively (that is, up to 53 °C and down to 15 °C final skin temperature reached for heat and cold studies, respectively).

High-threshold afferent fibers were selected from the population of axons,
functionally isolated in fine filaments dissected from median and ulnar nerves of macaque monkeys. The surgical and electrophysiological procedures as well as the methods and criteria used to identify and label primary skin afferent fibers with high thresholds have been described in detail elsewhere. The population of 20 fibers of the present study belongs in part to the larger one described in a previous paper, and in part to 8 additional experiments (total: 55 experiments) performed in an identical way on median nerves of macaque monkeys. The fibers studied in the present investigation were selected under the circumstances (a) that no stimulation had been applied to their receptive field prior to that used for their identification and study, and (b) that they responded within the period of stimulation (3 sec) in the range of temperature pulses used. No cold fibers, warm fibers, heat-sensitive cold fibers, or cold responsive low-threshold mechanoreceptors are included in this study. Mechanical pressure thresholds were determined at the most sensitive site using calibrated nylon filaments. The heat- and/or cold-threshold temperature was defined arbitrarily as the temperature evoking 3 impulses above background activity in the first 3 sec of stimulation. A series of measurements was taken before, during and after the study of each fiber to assess any effects of the stimuli delivered on the receptor. These included: (a) continuous monitoring of the background activity of the fiber during the interstimulus intervals (cumulated number of impulses every consecutive 10 sec period), and after the study; (b) measurement of mechanical and thermal thresholds before and after the study; and (c) a repeat single (that is, one stimulus per step) ascending series of stimulation in a few fibers. These measurements showed that no appreciable change of these parameters had occurred by the end of the study. Spontaneous activity decreased for about 20 sec after the application of high intensity heat stimuli but recovered and remained constant at its usual rate for the rest of the interstimulus interval, that is for 40 sec before the delivery of the next stimulus pulse. An important internal control was provided by the study itself in the very low variability of the responses which were obtained to successive identical stimuli at each intensity level during the course of the study.

Digital electronic counters and recorders were used for data collection. A PDP 11/20 minicomputer was used for the analysis of the data. Standard procedures of linear regression analysis were applied.

All the fibers studied belonged to high-threshold mechanothermal groups, that is they responded to both mechanical and thermal stimuli. The receptive fields were small areas of the skin (under 5 sq. mm) with one most sensitive spot and they were distributed evenly over the glabrous skin of the palm and the fingers.
**Heat studies.** Fifteen mechanothermal fibers were studied which responded to heat. They comprised 10 Aδ fibers with low conduction velocities (range: 2.1–14.0 m/sec, median: 4.1 m/sec; measured by direct electrical stimulation at the receptive field using a supramaximal stimulus) and 5 C fibers (range of conduction velocities: 0.8–1.2 m/sec). Ten fibers (6 Aδ and 4 C fibers) responded also to cold, in addition to mechanical and heat stimulation. Spontaneous activity at 39°C ranged for the fibers studied from 0 to 5.7 imp/sec with the median at 1.5 imp/sec.

Thirteen out of 15 fibers studied (87%) responded with linearly increasing frequency of discharge for stimuli up to at least an increment of 10°C. Nine of these continued to respond in a similar way to stimuli up to the maximum pulse delivered of 14°C (that is, up to 53°C final temperature). The response of the remaining 4 fibers of this group tended to saturate at various points above a 10°C stimulus pulse. Finally, the remaining fibers of the population (2 out of 15) responded with a positively accelerating frequency of discharge to stimuli of increasing intensity. Stimulus-response relations were analyzed after the spontaneous, ongoing activity (Ro) of a fiber was subtracted from its total response (R), to a stimulus pulse (S), and after the greatest stimulus pulse which evoked no response above any background activity (So) was similarly subtracted from the total stimulus pulse (S). These operations were thought necessary to describe the true dynamic response of a fiber to a series of stimulus pulses. Linear regression analysis was then applied to the stimulus-response relations: (a) without tranformation, (b) after log-log transformation, and (c) after semi-log transformation (that is, relating the response to the log of the stimulus). The coefficient of determination, r², was used as a quantitative measure of the linearity of the stimulus–response intensity functions which resulted. The mean value of r² (± 3 S.E.M.) was 0.928 ± 0.060 for untransformed data, 0.962 ± 0.024 for log-log transformed, and 0.854 ± 0.102 for semi-log transformed data. The exponent n of the power function \( R = K \cdot (S - So)^n \) was then obtained from the linear regression statistics of the log-log transformed data; its mean value (± 3 S.E.M.) was 1.23 ± 0.28, the median at 1.10, and the range of the exponents from 0.83 to 2.16. Stimulus-response intensity functions for all the fibers studied are shown in Fig. 2 in

![Diagram](image)

Fig. 2. Heat studies. Stimulus-response intensity functions for 15 mechanothermal Aδ and C fibers studied. R, Ro, S, So are explained in the text.
Fig. 3. Heat studies. Intrastimulus impulse counts of a fiber studied at different stimulus intensities. T-base: 39°C. Stimulus duration: 3 sec. Interstimulus interval: 60 sec. ON, OFF indicate stimulus onset and termination, respectively.

log-log coordinates. Intrastimulus time histograms revealed that the frequency of discharge increased gradually after an initial delay of 0.2-0.6 sec following stimulus onset and attained its maximum level without an overshoot. Cumulative intrastimulus impulse counts showed a more or less linear increase of the activity with time, after the initial delay, and a tendency for a positively accelerating increase with higher stimulus intensities. Data of such counts from one fiber are shown in Fig. 3 and pooled normalized data from 8 fibers in Fig. 4. The slopes of straight lines fitted to normalized data of cumulative intrastimulus impulse counts were very similar for different stimulus intensities for any one fiber, and for different fibers as well. Finally, no differences were found in the regime of Ad and C fibers studied.

Fig. 4. Heat studies. Intrastimulus cumulative impulse counts (mean ± S.E.M.) pooled from responses of 8 fibers to 0-14°C heating pulses starting from a baseline temperature of 39°C. The cumulated number of impulses of each fiber at each point shown in the graph has been normalized as percent of the total number of impulses cumulated at the end of stimulation period (3 sec) for the particular fiber, which is considered 100%. ON, OFF indicate stimulus onset and termination, respectively.
Cold studies. Five mechanothermal fibers were studied which responded to cold. All but one of these fibers belonged to the Aδ group (range of conduction velocities: 10.9–14.8 m/sec); the one C fiber had a conduction velocity of 1.1 m/sec. This C fiber responded also to heat; none of the 4 Aδ's responded to heat but they responded to both mechanical (high-threshold) and cold stimuli. The spontaneous activity at 30 °C was 0 for 3 fibers and 0.3 imp/sec for the remaining two. Linear regression analysis was applied to untransformed, log-log transformed and semi-log transformed data, as described above. The mean value of the coefficient of determination, r² (± 3 S.E.M.), was 0.953 ± 0.045 for untransformed data, 0.950 ± 0.037 for log-log transformed, and 0.913 ± 0.061 for semi-log transformed data. The mean exponent n (± 3 S.E.M.) for the power function (R − R₀) = K · (S − S₀)^n was 1.15 ± 0.037, the median at 1.17 and the range of the exponents from 0.90 to 1.58. Stimulus–response intensity functions for all the fibers studied are shown in Fig. 5 in log-log coordinates. Intrastimulus time histograms revealed that the frequency of discharge increased gradually after an initial delay of 0.2–0.6 sec. Cumulative impulse counts showed a linear increase of the activity with time, after the initial delay. The slopes of the straight lines fitted to normalized data of such counts were very similar for different stimulus intensities for any one fiber, as well as for different fibers.

This study provides information about the coding of the intensity of strong heat and cold stimuli in the discharge of high-threshold Aδ and C primary afferents which innervate the glabrous skin of the monkey hand. Stimulus–response intensity functions were fitted very well by power functions of the form (R − R₀) = K · (S − S₀)^n, for both fiber groups studied (Aδ and C) and modalities of thermal stimuli used (heat and cold). The values of the exponent n of such power functions ranged from 0.83 to 2.16, but for most functions n was a little over 1.0.

The present study was carried out on fibers which belonged to the high-threshold Aδ and C primary skin afferents. Convincing arguments from converging lines of evidence have been presented by Perl? to show that these fibers are intimately involved in the peripheral neural mechanisms subserving pain sensation. These fiber groups are "labeled lines"? for pain sensation, and it is through this perspective that the results of

![Fig. 5. Cold studies. Stimulus–response intensity functions for 5 mechanothermal fibers studied. R, Ro, S, So are explained in the text.](image-url)
this study acquire significance in relation to pain mechanisms. Psychophysical
stimulus–response intensity functions for heat pain have been described by Adair et
al.⁴. Interestingly, the range and the mean exponent of the power functions fitted to
their data are similar to those found in the present study. Both studies were made using
a 3 sec duration of stimulation, but other experimental variables, including a radiant
heat stimulator used in the psychophysical study, are quite different and make this
similarity difficult to assess.

A salient feature of a previous qualitative survey of the functional properties of a
large number of high-threshold primary afferents⁵ was the finding that high-threshold
Aα and C fibers do not differ in their qualitative sensitivity to noxious stimuli. The
present results suggest that these groups may not differ in their quantitative responses
to strong thermal stimuli as well. This finding lends further support to the hypothesis
proposed earlier⁶ that the different qualities of pain that seem to be evoked by afferent
activity when restricted to one or the other of these two sets of fibers must be
attributed to the supposition that they elicit quite different central actions.

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