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Sensitization of Unmyelinated Nociceptive Afferents in Monkey Varies With Skin Type

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SUMMARY AND CONCLUSIONS

1. Ninety-six C-fiber nociceptive afferents responsive to both mechanical and heat stimuli (CMHs) were studied in the monkey in an effort to determine what stimuli cause sensitization. Thirty-two of the fibers innervated glabrous skin (G-CMHs), while 64 innervated hairy skin (H-CMHs). Single-unit recording techniques were used.

2. The response to heat stimuli was studied with use of a laser thermal stimulator that provided stepped increases in skin temperature over a 7.5-mm-diameter area with rise times to the desired temperature near 100 ms for each stimulus. Changes in sensitivity were studied with a thermal test sequence (TTS), which consisted of 10 3-s stimuli presented with a 27-s interstimulus interval. The first stimulus was always 45°C. The remaining nine stimuli ranged from 41 to 49°C in 1°C increments and were presented in random order. The effects of stimulation with a more intense stimulus, 53°C for 30 s, were also determined.

3. The TTS stimuli were presented multiple times to the same fiber with a 10-min stimulus-free interval between runs. The H-CMHs were sensitized by the TTS stimuli, while the G-CMHs were not. Sensitization in the H-CMHs was manifest by a significant increase in the mean cumulative response to successive TTS stimuli, a significant decrease in thermal threshold, a significant increase in response to the first stimulus of each TTS run (viz., 45°C), and the development of spontaneous activity in certain of the H-CMHs. These changes in responsiveness were not observed in the G-CMHs.

4. Presentation of more intense stimuli (53°C for 30 s) caused further sensitization in many of the H-CMHs, but the effect was not significantly different from the change evoked by presentation of the TTS stimuli. The G-CMHs did not sensitize to the 53°C, 30-s stimulus (burn), and in most fibers suppression occurred, as measured by the response to the TTS stimuli 10 min after the burn. The suppression tended to be less marked 25 min after the burn.

5. The difference between H-CMHs and G-CMHs cannot be explained by a difference in the initial sensitivity of the two types of fibers. The mean responses to the initial 45°C stimulus of the first TTS run were similar: 10.3 ± 1.3 (SE) impulses for G-CMHs, and 9.8 ± 1.8 impulses for H-CMHs. The thermal thresholds, as measured by the response to the first TTS run, were also similar: 44.3 ± 0.3°C for G-CMHs, and 44.6 ± 0.2°C for H-CMHs.

6. The increased response to the TTS stimuli over successive runs for the H-CMHs tended to reach a plateau by the fourth run. The additional application of the burn in a few of these fibers failed to increase the response to TTS stimuli further.

7. In 10 H-CMHs, the duration of the TTS stimuli was changed from 3 to 1 s and runs were repeated after 10-min stimulus-free intervals. In contrast to the increased response evoked by 3-s stimuli, the mean response of the H-CMHs to the 1-s stimuli did not change significantly over successive runs.

8. Although the H-CMHs showed sensitization from one run to the next, within a run only suppression was evident. For ex-

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ample, the response to the second 45°C stimulus of the TTS in the first run was 31 ± 5% of the response evoked by the first 45°C stimulus within the same run.

9. The conduction velocity and receptive-field size of the H-CMHs and G-CMHs did not differ. However, the mechanical threshold of the H-CMHs (2.51 ± 0.11 bars) was significantly less than that of the G-CMHs (4.27 ± 0.32 bars, $P < 0.001$).

10. It is concluded that H-CMHs and G-CMHs differ significantly with regard to the propensity to sensitize to noxious heat stimuli. H-CMHs sensitize readily, and G-CMHs given the same stimuli do not sensitize. These results suggest that C-fiber nociceptive afferents do not play an important role in hyperalgesia in glabrous skin but may play an important role in hyperalgesia in hairy skin. This finding also supports the hypothesis that A-fiber nociceptive afferents play an important role in explaining the marked hyperalgesia that is produced by a substantial thermal injury (53°C for 30 s) to the glabrous skin of the hand (22).

INTRODUCTION

Hyperalgesia is a term that denotes the striking alteration in pain sensibility that occurs with injury to the skin, inflammation, and certain nerve injuries. There is now evidence that the neural mechanism of hyperalgesia following cutaneous injury is based on changes in the responsiveness of peripheral nociceptive receptors. This change, termed sensitization, is associated with a decrease in threshold, an increased response to suprathreshold stimuli, and often, spontaneous activity.

Previous investigators using a variety of paradigms have had varying success in producing sensitization in C-fiber nociceptive afferents (1–5, 7–10, 12–15, 17–22, 25–28). One important variable that may explain such discrepancies is the stimulus paradigm used. If stimuli are applied at short interstimulus intervals, such that suppression dominates, or if stimuli are too strong, such that the receptor is damaged, sensitization may not be observed.

In this paper we present evidence that the propensity for sensitization in C-fiber nociceptive afferents varies with the type of skin innervated by the receptor as well as with the intensity of the stimuli. Sensitization in monkey is a prominent and consistent property of C-fiber nociceptors that innervate hairy skin, while sensitization appears to occur weakly if at all in C-fiber nociceptors that innervate glabrous skin. It is suggested that A-fiber nociceptive afferents may be more important in explaining hyperalgesia that occurs with major injury to the glabrous skin (22), while both C and A nociceptive afferents probably play a role in explaining hyperalgesia in the hairy skin. Preliminary results have been presented (6).

METHODS

Action-potential activity in single primary afferents was recorded from the ulnar, median, medial antebrachial cutaneous, saphenous, and sural nerves of *Macaca fasicularis* and *Macaca mulatta* monkeys. The monkeys were initially sedated by intramuscular injection of ketamine and then anesthetized to a level at which the corneal reflex was absent by intravenous administration of sodium pentobarbital. Core temperature was measured by a rectal probe and maintained at 38 ± 1°C with the use of a heating pad. At the beginning of each experiment, Bicillin was administered for prophylaxis against infection.

The teased-fiber technique for single-fiber recordings was used as previously described (7, 19). A block diagram of the experimental apparatus is shown in Fig. 1. The microvolt action-potential signals were amplified by a low-noise differential preamplifier (Princeton Applied Research model 113). The output of the amplifier was filtered by a Kronhite variable band-pass filter to optimize the signal-to-noise ratio for a given action potential and then was filtered by a 60-Hz notch filter to minimize "line" noise. A differential amplitude and time discriminator (Midgard model TVA-1) was used in order to record only the action potential of interest. The action-potential signal was monitored visually via an oscilloscope (along with the time and voltage windows) and aurally via a speaker. The discriminator provided a digital pulse to the computer for every neural signal that fell within both the amplitude and time windows. The complete experiment was under the control of a PDP-11/34 computer. The computer turned on the constant-temperature stimulator (to be described below) at prescribed intervals and monitored the applied stimulus. The computer displayed on a video terminal the total neural impulse counts for designated time intervals during the experiment (e.g., for the interval during which the stimulus is on), and also stored the time in-

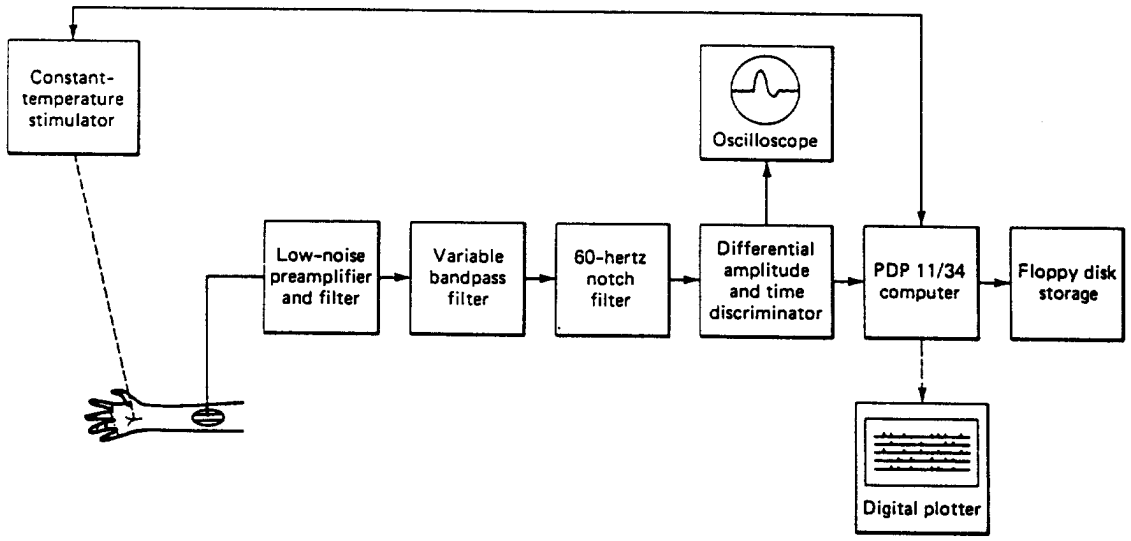

FIG. 1. Schematic diagram of the recording procedures.

tervals between neural spikes as well as other data pertaining to the stimulus profile on a floppy disk. In addition, the computer was used off-line to generate replicas of the time course of action potentials as well as appropriate histograms with the aid of a digital plotter.

Constant-temperature stimulator

A laser thermal stimulator (24) was used to deliver stepped increases in skin temperature to the receptive field of the fiber under study. A carbon dioxide infrared laser (10.6-μm wavelength) that uniformly heated a 7.5-mm-diameter spot was controlled by a radiometer that remotely sensed skin temperature. In this way the temperature of the stimulated area could be raised to the desired level for a variable length of time. A visible helium-neon laser, which was colinear with the infrared laser and the radiometer, was used for localizing the stimulation spot. Using this device, stepped increases in skin temperature could be achieved with rise times of 80–140 ms and with an accuracy of ±0.1°C.

Experimental protocol

Nociceptive afferents were identified initially by their responses to firm squeezing of the skin with two fingers. The shape of the receptive field was then mapped on the skin with dye at spots where the fiber responded to a 0.55-mm-diameter nylon monofilament, which exerted a force of 21 g. After waiting several minutes, the threshold response to mechanical stimulation was determined using nylon monofilaments (von Frey type). Next, a small piece of ice was placed on the receptive field for 20 s to test for a response to cooling. Five to 10 min elapsed without further stimulation before initiation of the first experimental run. The different types of experimental runs are described in the RESULTS section. At the end of the experiment, the conduction velocity was estimated from measurements of the latency of response to suprathreshold electrical stimuli applied to the receptive field with intradermal electrodes and from measurements of conduction distance determined by the length of a piece of suture placed along the path of the nerve between the receptive field and the recording electrode.

RESULTS

Static properties

A total of 96 C-fiber nociceptive afferents responsive to mechanical and heat stimuli (CMHs) were studied. Thirty-two of the fibers innervated glabrous skin (G-CMHs), while 64 innervated hairy skin (H-CMHs). The static properties of the G-CMHs and H-CMHs are listed separately in Table 1. The mechanical threshold of the H-CMHs (2.51 ± 0.11 bars) was significantly less than that of the G-CMHs (4.27 ± 0.32 bars, $P < 0.001$, $t = 5.31$). The initial thermal threshold, receptive-field area, and conduction velocity of G-CMHs did not differ significantly from those of H-CMHs.

Although we did not routinely test for a response of the CMHs to chemicals, 13 of 16 tested responded to application of histamine, papain, or cowage to their receptive fields. Therefore, these CMHs are probably not functionally different from polymodal C-fi-

TABLE 1. *Comparison of glabrous and hairy skin C-fiber nociceptive afferents responsive to heat and mechanical stimuli*

Property	Glabrous Skin	Hairy Skin
No. of fibers studied	32	64
Receptive field, mm^2	28.3 ± 2.6 (32)	26.0 ± 1.7 (64)
Conduction velocity, m/s	0.79 ± 0.03 (24)	0.83 ± 0.03 (43)
Mechanical threshold, bars*	4.27 ± 0.32 (32)	2.51 ± 0.11 (64)
Heat threshold, °C	44.3 ± 0.3 (20)	44.6 ± 0.2 (31)
Response to 1st thermal stimulus, 45°C, 3 s	10.3 ± 1.3 (20)	9.8 ± 1.8 (31)

Values are means ± SE. Numbers in parentheses are *n*. * Glabrous and hairy were significantly different, $P < 0.001$, $t = 5.31$.

ber nociceptive afferents described by others (3–5, 8, 10, 12, 14, 15, 17, 19, 21, 28).

Response to 41–49°C stimuli

A thermal test sequence (TTS) was applied to the receptive fields of the CMHs in order to compare the responses of G-CMHs and H-CMHs. Each TTS run consisted of 10 stimuli that were 3 s in duration. The interval between stimuli was 27 s. The first stimulus of a run was always 45°C and the remaining nine stimuli ranged in intensity from 41 to 49° in 1°C increments and were presented in random order, with the constraint that each stimulus was presented only once. In addition to being presented on the first trial, the 45°C stimulus was presented a second time as part of the random matrix. Six different random matrices were used in this study. The order of the stimuli was balanced to minimize interaction effects. The results were similar for each of the random sequences used. The temperature between stimuli and for 1 min before the TTS was maintained at 38°C.

The cumulative evoked response of a fiber, defined as the total number of action potentials from the fiber in response to all the stimulus temperatures within a single TTS, was used as a measure of the responsiveness of the fiber. The mean cumulative evoked response of the G-CMHs and H-CMHs to the TTS stimuli for each of three successive runs is shown in Fig. 2. A 10-min stimulus-free interval occurred between the runs. The response of the H-CMHs increased significantly from run 1 to run 3 ($P < 0.01$, see description of statistical analysis below), while that of the G-CMHs failed to change significantly across the three runs.

The data were analyzed using a mixed-model hierarchal two-way analysis of variance (16). The analysis was performed only for data on fibers that had at least three TTS runs in succession. The effects of skin type interacted significantly with run number ($F = 4.8$, df = $^2/_{30}$, $P < 0.025$). The Duncan multiple-range test was used to test differences between means. The mean response of the H-CMHs increased significantly from 57 impulses on run 1 to 104 impulses on run 3 ($P < 0.01$).

There were few exceptions to the observation that H-CMHs sensitize and G-CMHs do not. Of the 29 H-CMHs that received at least two TTS, only 5 failed to have an increased response in run 2 as compared to run 1. Of the 20 G-CMHs given at least two TTS, only 3 had an increased response in run 2 as compared to run 1.

The response to each of the TTS temperatures as a function of run number for the H-CMHs is shown in Fig 3*A* (the response to the first stimulus, 45°C, is not presented here but is presented later). It is evident that the increased response of the H-CMHs to repeated presentations of the TTS stimuli occurred at each of the temperatures for which a response was observed. Moreover, the shape of the stimulus-response function appears not to have changed. The response of the G-CMHs to each of the TTS temperatures for runs 1 and 2 is shown in Fig. 3*B*. The response did not change notably at any of the temperatures.

The increased response of the H-CMHs to suprathreshold stimuli was accompanied by a significant decrease in the thermal threshold over successive runs. In Fig. 4, the mean thermal threshold of H-CMHs and G-CMHs is plotted as a function of run number.

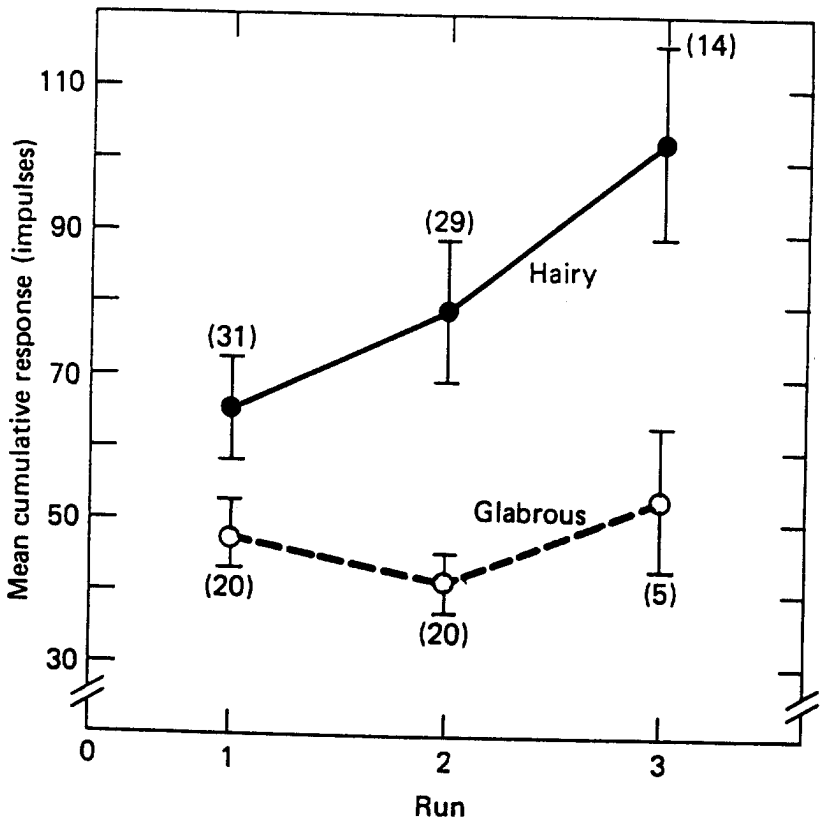

FIG. 2. Mean cumulative response of hairy skin (H-CMHs) and glabrous skin (G-CMHs) C-fiber nociceptive afferents to the thermal test sequence (TTS) as a function of run number. The first stimulus of the TTS was always 45°C. The remaining nine stimuli ranged from 41 to 49°C in 1°C increments and were presented in random order. The stimuli were 3 s in duration and were presented every 30 s. Each run was separated by a 10-min stimulus-free interval. For fibers innervating hairy skin (solid line) the cumulative response increased significantly (sensitized) with repeated runs, whereas for glabrous skin the response did not change significantly. Number of fibers tested in parentheses.

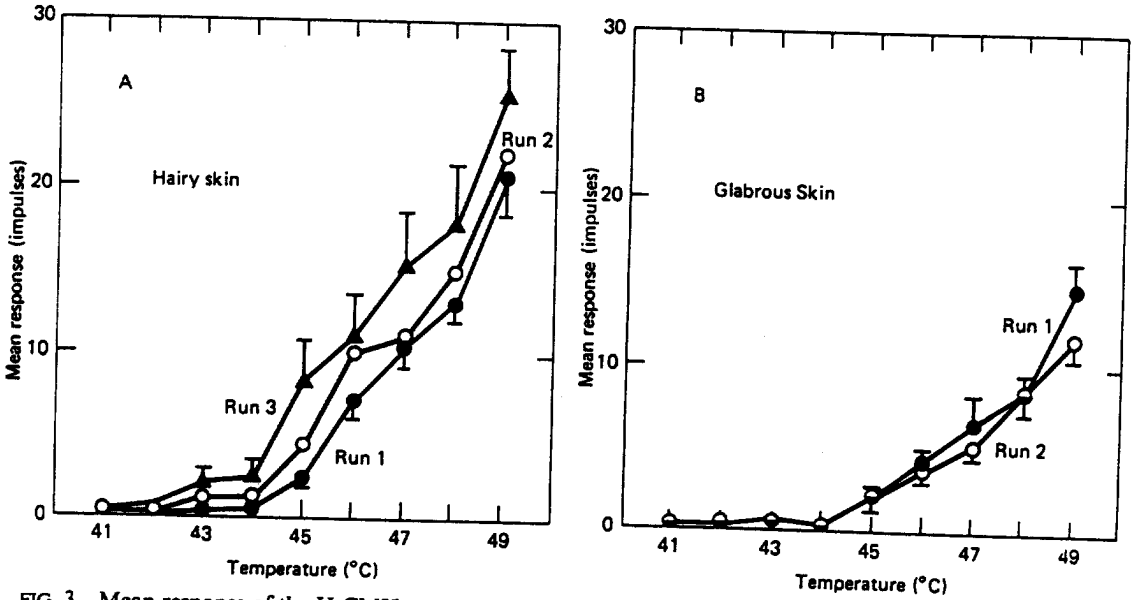

FIG. 3. Mean response of the H-CMHs and G-CMHs as a function of stimulus temperature for successive runs. The response to the first stimulus (the first 45°C stimulus) was deleted from this analysis. The response increased monotonically as a function of stimulus temperature for both fiber types. *A*: stimulus response function increased as a function of run number for the H-CMHs. *B*: response of G-CMHs failed to change as a function of run number. Stimulus parameters were the same as for Fig. 2.

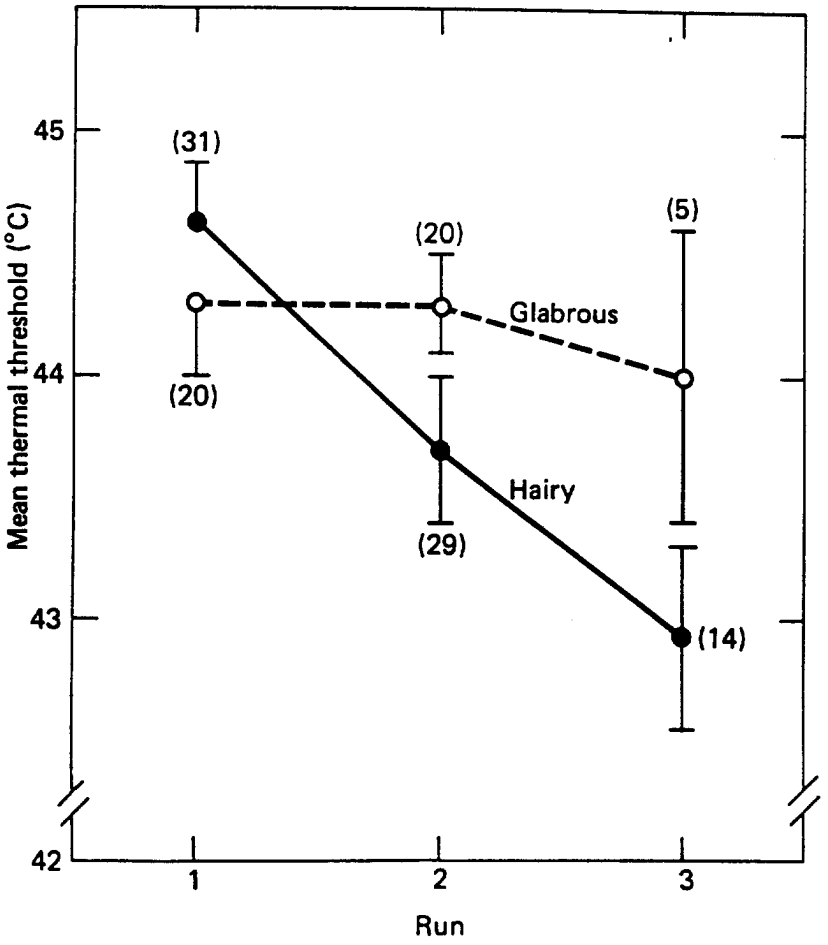

FIG. 4. Mean thermal threshold of the C-fiber nociceptive afferents for successive runs of the TTS sequences. The mean thermal threshold of the H-CMHs decreased as a function of run number, whereas it did not change significantly for the G-CMHs. Stimulus parameters were the same as for Fig. 2. Threshold was defined as the lowest temperature that evoked at least one response.

Threshold was defined as the lowest temperature in the TTS at which at least one impulse occurred. The threshold of the G-CMHs did not change significantly over the three runs, as is also shown in Fig. 4. Of the 29 H-CMHs that received at least two TTS, 13 had a lower thermal threshold in run 2 compared to run 1. In contrast, only 2 of 20 G-CMHs had a lower thermal threshold in run 2.

A one-way hierarchal mixed-model analysis of variance was performed on the threshold data for H-CMHs that received three successive TTS runs. The threshold changed significantly as a function of run number ($F = 6.23$, df = $^2/_{22}$, $P < 0.01$). The individual means were compared with use of the Duncan multiple-range test. The mean threshold on run 3, 42.9°C, was significantly less than the threshold on run 1, 44.3°C ($P < 0.01$).

The first stimulus of each TTS was 45°C. The sensitization of the H-CMHs was reflected in particular by a significant increase in the response to this stimulus. The response of each fiber to the first 45°C stimulus of each TTS was normalized by dividing by the response of that fiber to the first 45°C stimulus of run 1. The mean of this normalized response was then calculated separately for G-CMHs and H-CMHs. The results are plotted in Fig. 5. The results for run 1 are not shown, since this value is by necessity 1. The response of the H-CMHs increased from run 1 to run 3 such that by run 3 the mean response was nearly 3 times that of run 1. The response of the G-CMHs on runs 2 and 3 failed to differ from that on run 1.

The distribution of ratios of the response on run 3 to run 1 was skewed, and therefore a nonparametric Wilcoxon signed-ranked test was cho-

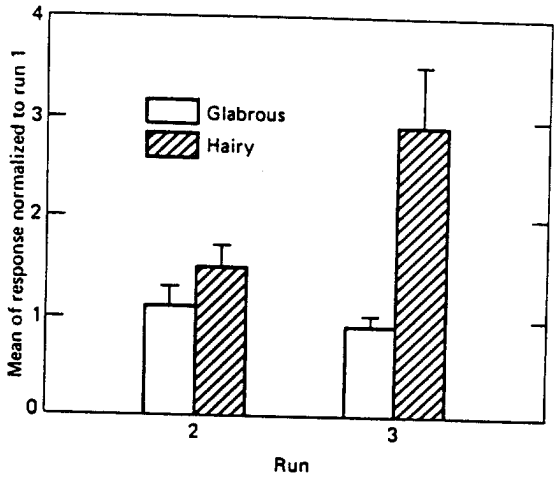

FIG. 5. Mean normalized response of the C-fiber nociceptive afferents to the initial 45°C stimulus of the TTS sequence for successive runs. The response of a fiber was normalized by its response to the initial 45°C stimulus of the first run. The response of the H-CMHs increased significantly by the third run, whereas the response of the G-CMHs failed to change.

sen for analysis. The response in run 3 was greater than the response in run 1 in all but one of the 14 H-CMHs, thus the response in run 3 was significantly greater ($P < 0.01$).

The mean response to the first 45°C stimulus of run 1 for the G-CMHs (10.3 ± 1.3 impulses) was similar to that of the H-CMHs (9.8 ± 1.8 impulses). Thus the initial thermal sensitivity of G-CMHs and H-CMHs was similar. This is further supported by the observation that the thermal threshold of G-CMHs and H-CMHs on run 1 was similar (see Table 1).

In seven H-CMHs the TTS stimuli were presented multiple times to determine at what point sensitization would cease. As before, a 10-min stimulus-free interval occurred between runs. Plots of the cumulative response as a function of run number for each of these fibers are shown in Fig. 6. Despite considerable interfiber variability, the response reached a plateau in most cases by the fourth presentation of the TTS stimuli.

To determine whether the difference in H-CMHs and G-CMHs with regard to sensitization was truly due to type of skin, other factors were considered. It was found that the skin temperature prior to the initial thermal stimulation tended to be higher in the glabrous skin. We were unable to demonstrate, however, any relation between sensitization and skin temperature or core temperature. We also tested whether sensitization varied as a function of the distance of the receptive field from the spinal cord or as a function of whether the receptive field was located on the hindlimb versus forelimb, and again we failed to demonstrate any correlation.

Response to short-duration stimuli

We wished to determine if less-intense stimuli also sensitized the H-CMHs. A modified TTS was delivered to the receptive field of 10 H-CMHs. Parameters were identical to that of the previously described TTS except that 1 s (instead of 3 s) duration stimuli were used. The runs were administered 3 times, with 10-min stimulus-free intervals between runs. The mean cumulative responses of the H-CMHs to the 1- and 3-s stimuli are plotted as a function of run number in Fig. 7. Unlike that for the 3-s stimuli, the response to the 1-s stimuli did not change significantly as a function of run number. Moreover, the thermal threshold to the 1-s stimuli did not change (mean threshold of 44.7°C for runs 1 and 3) and none developed spontaneous activity. As expected, the cumulative response to the 3-s stimuli for each run was significantly greater than that for the 1-s stimuli ($P < 0.01$, see below).

The mixed-model hierarchal two-way analysis of variance was chosen for the statistical analysis. The effects of duration on response varied significantly as a function of run number ($F = 6.28$, df $= {}^{2}/_{40}$, $P < 0.01$).

Response to intense noxious stimuli

Given that the 3-s TTS stimuli sensitize the H-CMHs, what happens if more intense thermal stimuli are applied? To answer this, 53°C, 30-s stimuli were applied to 11 H-CMHs as well as to 11 G-CMHs. The TTS stimuli were applied twice before and twice after this burn stimulus to monitor changes in thermal sensitivity. In the case of five H-CMHs, the TTS stimuli were applied in place of the burn, which allowed the effects of the burn to be compared to effects produced by the TTS stimuli. A 10-min stimulus-free interval separated all runs.

In Fig. 8, the mean cumulative response of the G-CMHs and H-CMHs to the TTS

FIG. 6. (same as for was consid a plateau ir

stimuli is the two five H-C uli). The in respor test, $t = 4$ H-CMHs first to th the respo to the 53 nificantly that were the 53°C.

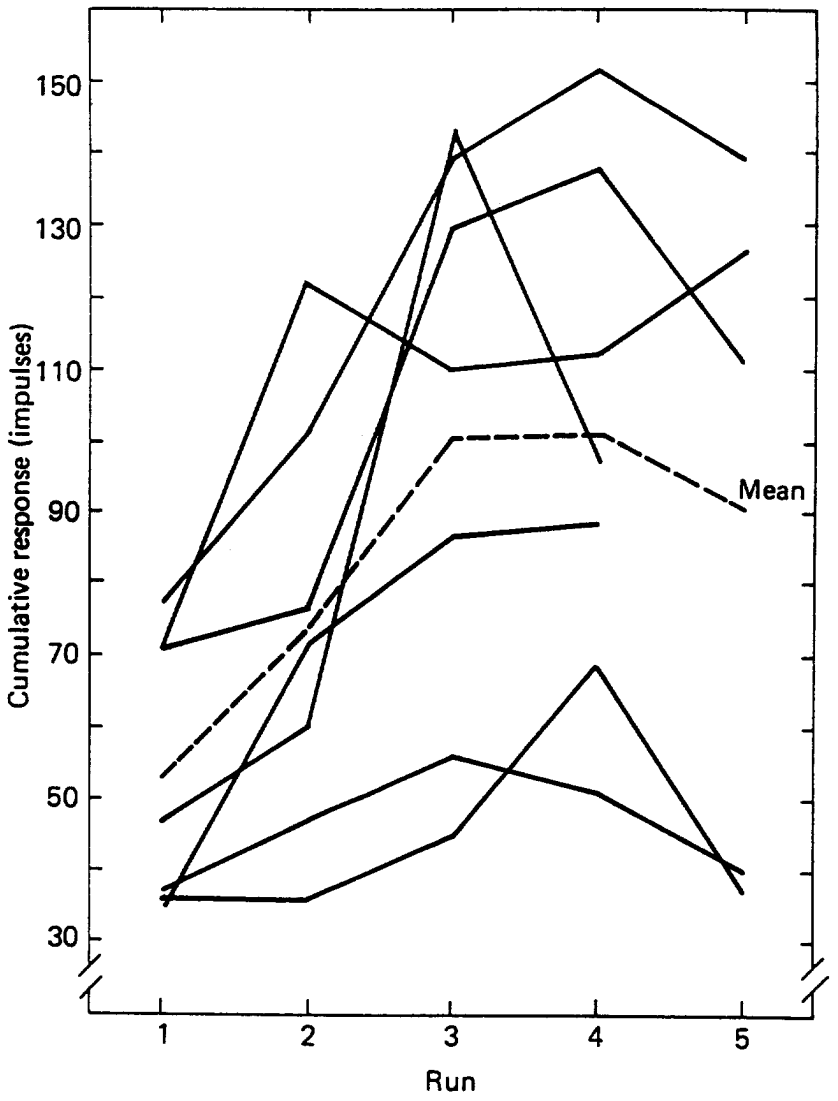

FIG. 6. Cumulative response of seven H-CMHs for each of five successive runs. Stimulus parameters are the same as for Fig. 2. The dashed line represents the mean cumulative response for these seven fibers. Although there was considerable variability among fibers, the cumulative response increased during the first three runs and reached a plateau in all but one case by the fourth run.

stimuli is plotted for the two runs before and the two runs after the burn (in the case of five H-CMHs, before and after the TTS stimuli). The G-CMHs had a significant decline in response after the burn (match-paired t test, $t = 4.76$, $P < 0.001$). The response of the H-CMHs increased significantly from the first to the last run ($t = 3.08$, $P < 0.01$), and the response of the fibers that were exposed to the 53°C, 30-s stimulus did not differ significantly from the response of the H-CMHs that were presented with the TTS in place of the 53°C, 30-s stimulus. Thus the 53°C, 30-s burn did not result in greater sensitization of the H-CMHs than the TTS stimuli.

Fifty percent of the H-CMHs developed spontaneous activity in the course of sensitization. This was not observed in G-CMHs. The spontaneous activity was particularly apparent after the 53°C, 30-s stimulus.

Response suppression

We previously reported (19) that response suppression was a prominent property of CMHs. Although H-CMHs show signs of sensitization from one run to the next,

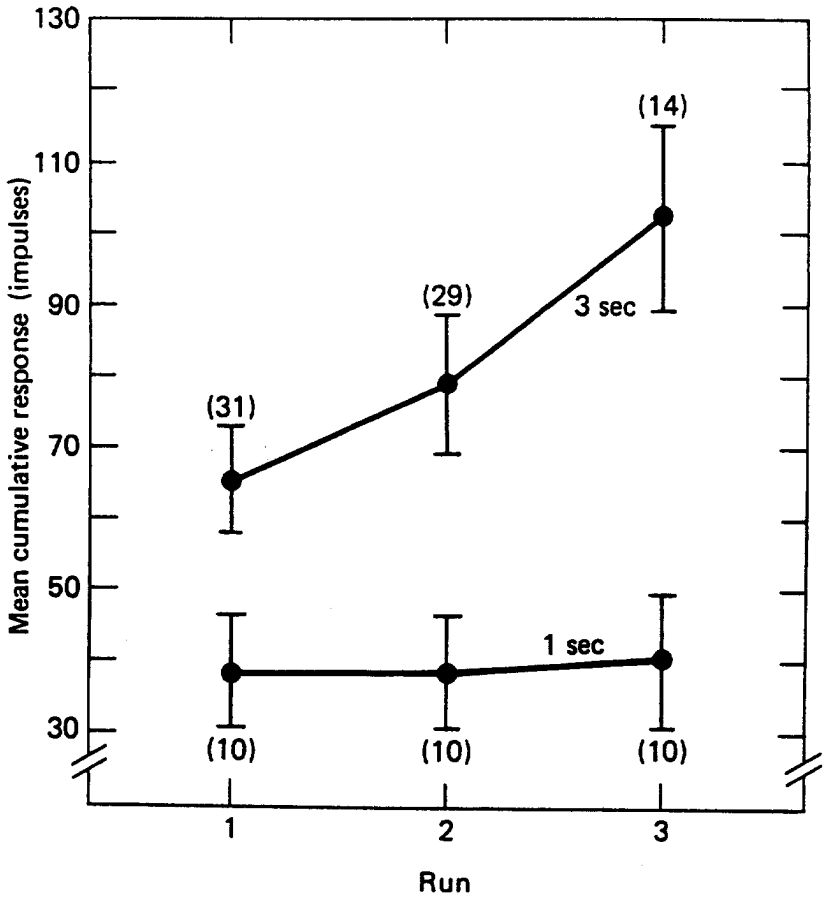

FIG. 7. Mean cumulative response of C-fiber nociceptive afferents that innervated hairy skin as a function of run for 1 and 3 s duration TTS stimuli. Other stimulus parameters were the same as for Fig. 2. In contrast to the response to the 3 s duration stimuli, the mean cumulative response did not increase significantly for successive runs when 1 s duration stimuli were delivered.

suppression within a run was marked. As an example of this, the responses to the two 45°C stimuli in run 1 were compared in both G-CMHs and H-CMHs. The 45°C stimulus was delivered as the first stimulus in the TTS sequence and also as one of the nine subsequent stimuli. The response to the second 45°C stimulus taken as a ratio of the response to the first 45°C stimulus was 0.31 ± 0.05 (n = 27) for the H-CMHs and 0.22 ± 0.04 (n = 20) for the G-CMHs. This 70–80% reduction in response during a run was comparable to that reported previously (19).

A further example of response suppression of an H-CMH in the process of being sensitized is shown in Fig. 9. This fiber was stimulated with 28 3-s stimuli that ranged in intensity from 45 to 49°C in 1°C increments. The stimuli were given every 30 s in pseudorandom order. The first three stimuli were 47°C and data from these trials were deleted from the analysis. The remaining 25 stimuli consisted of five presentations of each of the temperatures from 45 to 49°C. Each stimulus temperature was preceded once by every other stimulus temperature. The mean response to each of the 45–49°C stimuli was determined and these values are plotted in Fig. 9. In addition, the mean response is shown separately when the preceding stimulus intensity was high (48, 49°C) and when it was low (45, 46°C). The response was greater when the previous stimulus was low in intensity rather than high in intensity, thus suggesting that response suppression varies directly with the intensity of the preceding

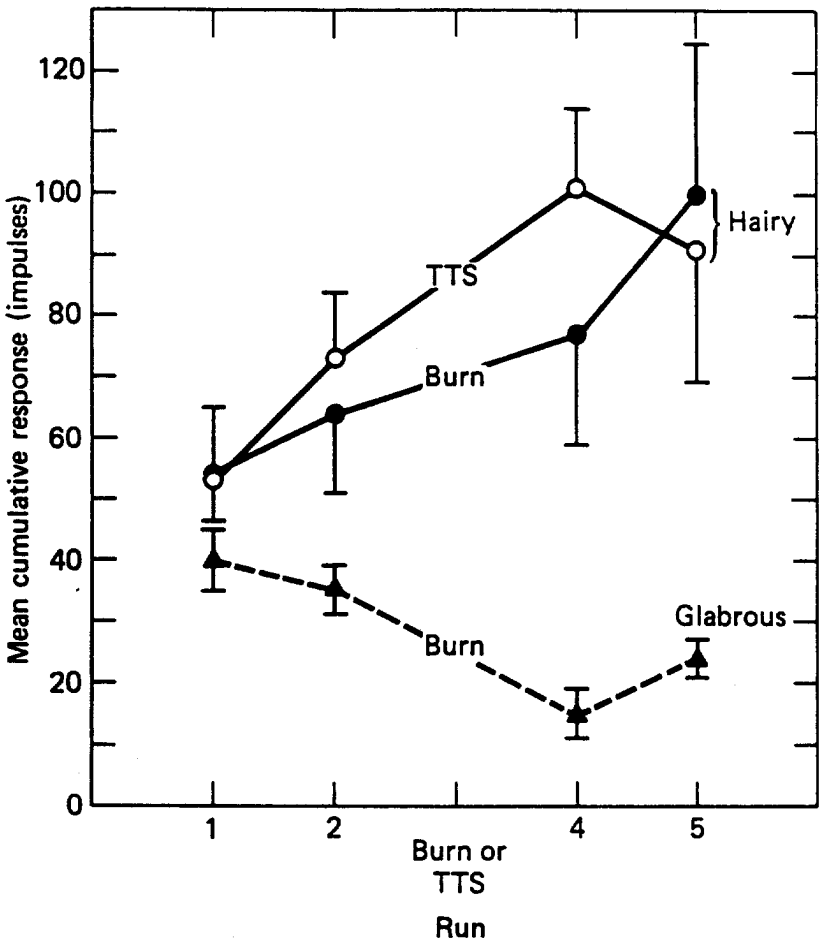

FIG. 8. Mean cumulative response of C-fiber nociceptive afferents as a function of run. The third run consisted of either a 53°C, 30-s burn or a standard TTS sequence, as indicated. All other stimulus parameters are the same as for Fig. 2. For hairy skin, responses following the burn were not significantly different from those following the TTS sequence. For glabrous skin, the response was significantly reduced following the burn.

stimulus. Sensitization was presumably ongoing in this fiber as manifest by a marked increase in response to the TTS after as compared to before the 28 45–49°C stimuli. Thus response suppression is a prominent property of H-CMHs even when these fibers are in the process of being sensitized.

Quickly adapting versus slowly adapting response to stepped thermal stimuli

We determined previously (23) that H-CMHs exhibit either a quickly adapting or a slowly adapting response to step (<140-ms rise time) increases in skin temperature. When these CMHs are subdivided into two classes based on this temporal response to heat stimuli, other properties of the two classes were also found to differ. However, these two subclasses of H-CMHs did not differ significantly in terms of their magnitude of sensitization.

Though the H-CMHs are readily subclassified into a quickly adapting (37 of 64) versus slowly adapting (27 of 64) response, the distinction is not as obvious for G-CMHs. Although most G-CMHs could be classified as either quickly adapting (8 of 32) or slowly adapting (17 of 32), several (7 of 32) exhibited characteristics of each class. The failure to sensitize was equally evident in quickly adapting G-CMHs and slowly adapting G-CMHs.

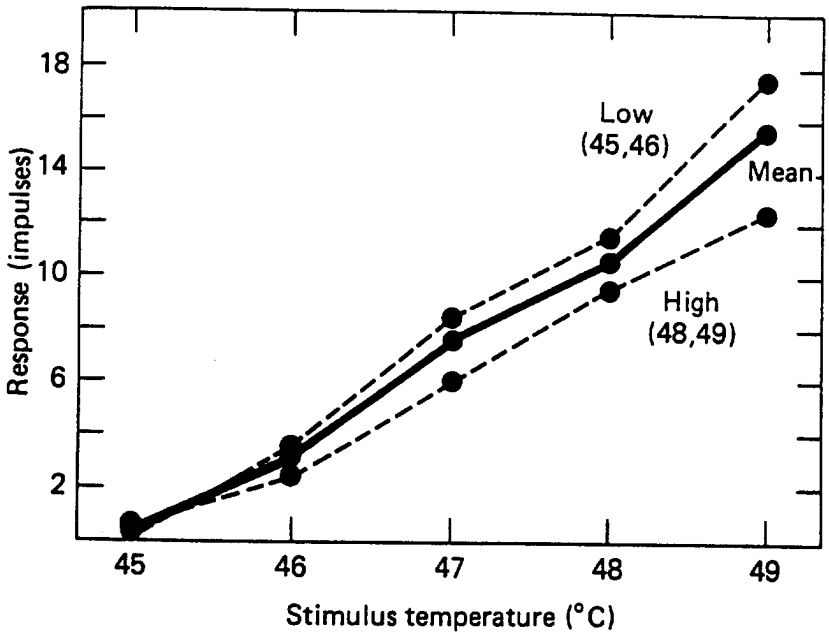

FIG. 9. Response of a C-fiber nociceptive afferent that innervated hairy skin as a function of stimulus temperature. The thermal sequence consisted of 28 stimuli of 3 s duration presented every 30 s. The first three stimuli were 47°C and were not included in this analysis. The remaining stimuli ranged in intensity from 45 to 49°C in 1°C increments and were presented in random order, with the constraint that each temperature was presented 5 times and was preceded by every other temperature once. The dashed lines give the mean response at a given temperature when the preceding stimulus was either a low temperature (i.e., 45 and 46°C) or a high temperature (i.e., 48 and 49°C). The solid line is the mean response for all stimuli. The response to a given temperature was higher when preceded by the low temperatures than when preceded by the high temperatures.

DISCUSSION

Comparison of hairy versus glabrous skin

Sensitization has been described for both A- and C-fiber nociceptive afferents in cat, rabbit, monkey, and man (1–14, 17–21, 23–27). The receptive field of the fibers described in most instances was located on hairy skin. In cases where both glabrous and hairy skin were studied, a distinction was not always made between results obtained from the two skin types. The results presented here indicate that CMHs with receptive fields on hairy skin (H-CMHs) became sensitized following intense heat stimuli, whereas CMHs with receptive fields on glabrous skin (G-CMHs) did not. This sensitization of the H-CMHs was characterized by the following observations: *1*) the overall response to 41–49°C, 3-s thermal test stimuli (TTS) increased significantly over three runs delivered at 10-min intervals, *2*) this increase was manifest at each of the temperatures used to test sensitivity (41–49°C) and was particularly prominent for the first stimulus in the TTS (viz., 45°C), *3*) the increase in responsiveness was accompanied by a significant drop in heat threshold, and *4*) many of the fibers displayed spontaneous activity after but not before sensitization. The G-CMHs failed to display any of these characteristics of sensitization.

The reason for this discrepancy between H-CMHs and G-CMHs is unclear. It appears not to be associated with a difference in the initial thermal sensitivity of the two types of fibers. The initial thermal threshold as well as the response to the first thermal stimulus (viz., 45°C) did not differ. While a difference in the H-CMH and G-CMH receptor itself may be present, it is also possible that the immediate milieu of the two receptor types differs so as to favor the development of sensitization in H-CMHs. Additional evidence supporting this is the observation that nociceptive A-fibers in monkey also appear to sensitize more readily in hairy than glabrous skin (20; unpublished observations). There was no correlation between the degree of sensitization of CMHs and distance of the receptive field from the spinal cord. The tem-

perature of the receptive field and core temperature prior to application of the first heat stimulus appeared also not to influence sensitization.

Suppression and deactivation

Though H-CMHs sensitize, suppression is prominent when stimuli are given at closely spaced intervals (e.g., 30 s). This point, emphasized by many investigators (3, 4, 17, 19, 20), explains why sensitization may not be observed in all experimental paradigms. Deactivation as a result of too strong an injury (4, 5) has also been mentioned as a factor that might result in the property of sensitization in nociceptive fibers being overlooked. The 53°C, 30-s burn stimulus caused suppression in G-CMHs. This suppression appeared to diminish with time, thus suggesting that permanent injury of the receptor was not a factor in the suppression.

Neural mechanism of hyperalgesia

The results of this investigation suggest that the neural mechanism of hyperalgesia should be considered separately for hairy skin and glabrous skin of the hand. We previously compared the response of C- and A-fiber nociceptive afferents in monkey with the subjective responses of humans when each were exposed to a 53°C, 30-s stimulus applied to the glabrous skin of the hand (22). The G-CMHs showed only suppression, while the A-fiber nociceptive afferents sensitized markedly. Thus it is likely that the A-fibers account chiefly for the marked hyperalgesia that results from a 53°C, 30-s burn to the glabrous skin. However, LaMotte et al. (20) determined that G-CMHs showed a slight decrease in thermal threshold following a 50°C, 100-s burn applied to the hand. Notably, the response to suprathreshold stimuli did not change significantly (R. H. LaMotte, personal communication). In the study presented here, the G-CMHs showed neither an increased response to suprathreshold stimuli nor a decreased threshold following injury. Because there were differences in the stimulus paradigms between this study and the study of LaMotte et al. (20), the possibility that G-CMHs play at least some role in hyperalgesia, particularly with mild injuries, cannot be excluded.

For hairy skin, both A-fiber (unpublished observations) and C-fiber nociceptive afferents become sensitized following a major thermal injury and thus may play a role in hyperalgesia. LaMotte et al. (20) found that following a minor thermal injury (50°C, 100-s stimulus) to the hairy skin, hyperalgesia occurred in human subjects. The H-CMHs that they studied showed both a drop in threshold (20) and an increased response to suprathreshold stimuli (18). The A-fiber nociceptive afferents failed to sensitize. Thus, H-CMHs appear to play a major role in coding for hyperalgesia following a minor injury to the hairy skin. The relative role of A-fiber nociceptive afferents and H-CMHs in coding for the hyperalgesia following a major thermal injury to the hairy skin remains to be determined.

The data presented here underscore the importance of distinguishing differences in fiber types on the basis of the type of skin innervated. There does not appear to be a simple, uniform neural mechanism of hyperalgesia. The magnitude of injury and the type of skin may each prove to be important variables when considering the fiber types that code for hyperalgesia.

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