

Excitability changes in peripheral nerve fibers after repetitive electrical stimulation

Implications in pain modulation

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The Melzack-Wall gate control theory has been invoked to explain the peripheral analgesia resulting from repetitive electrical stimulation of peripheral nerve. This model emphasizes presynaptic inhibitory interactions among afferent fiber terminals in the spinal cord. An alternative explanation, that of velocity change in peripheral nerve fiber conduction, has been suggested by compound action potential studies from our laboratory. The present study was designed to extend this work, and to investigate the single fiber changes subsequent to brief (5- to 20-minute) periods of repetitive, high frequency (180 to 200/sec) electrical stimulation through an implantable peripheral nerve cuff device of the type used clinically for pain relief. Most fibers, regardless of their diameter (estimated from conduction velocity), show one or more of the following characteristics: a transient slowing of conduction velocity, an increase in electrical threshold and/or a decrease in response probability following a period of repetitive electrical stimulation. This supports the hypothesis that there are changes in direct peripheral nerve fiber excitability occurring under conditions simulating clinical electroanalgesia.

KEY WORDS • electroanalgesia • peripheral nerve fiber • excitability change • pain relief

REPETITIVE electrical stimulation of a peripheral nerve has proved to be an effective treatment for certain types of pain resulting from peripheral neuropathies,^{8-11,14,16,19,24} and for acute, postoperative incisional pain.⁵ The Melzack-Wall gate control theory¹³ was originally invoked to explain these clinical results. The Melzack-Wall model emphasizes presynaptic inhibition of small-diameter afferent fiber input (nociceptive) by large-diameter afferent fiber input (non-nociceptive) at the level of the spinal cord dorsal horn. Since this model was proposed, several of the neurophysiological predictions inherent in it have not been confirmed.¹⁵ For example, the model predicts that selective small-fiber (A-delta and C) input should produce primary afferent hyperpolarization (PAH) recorded as an antidromically conducted positive dorsal root potential (DRP)

from dorsal root fibers, a disfacilitation of primary afferent fiber terminals. However, several investigators have not been able to confirm PAH resulting from pure small-fiber afferent input.^{4,7,18,26,27}

An alternative explanation for peripheral electroanalgesia, that of electrical excitability change in peripheral nerve fiber, has been advanced by several laboratories,^{2,20-22} including our own.⁶ In an earlier study from our laboratory,⁶ compound action potential components of the sensory nerve were reversibly suppressed in cats by repetitive electrical stimulation of the nerve. The sural nerve in these experiments was severed distal to the dorsal root ganglion, thereby precluding any participation by antidromically conducted activity (dorsal root potentials).

The present study was designed as an extension of our previous work. It investigates single-fiber ex-

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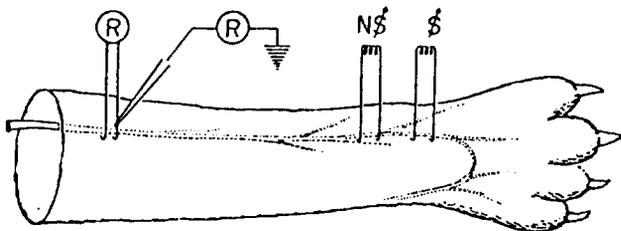


FIG. 1. Schematic diagram of experimental setup. Three pairs of Ag-AgCl wire electrodes were placed on the exposed superficial radial nerve: control stimulation electrodes (S) for application of single pulses through a constant-current stimulator, test stimulating electrodes (NS) for application of repetitive pulses through the neurostimulator unit, recording electrodes for monitoring the nerve compound action potentials. Single-fiber recordings were made through a glass micropipette at the site of the compound action potential recording electrodes.

citability changes underlying the compound action potential changes of the peripheral nerves after short periods of repetitive electrical stimulation through an implantable cuff device of the type used clinically for pain relief. Excitability was measured in terms of conduction velocity and electrical threshold.

Materials and Methods

Experiments were performed on domestic cats weighing 2.5 to 4.0 kg, anesthetized with an intraperitoneal injection of sodium pentobarbital (45 mg/kg). Supplemental intravenous injections of a mixture of alpha-chloralose (50 mg/kg) and urethane were administered as needed to maintain adequate anesthesia as judged by corneal reflex, pupil diameter, heart rate, and blood pressure. Tracheal intubation, and femoral venous and femoral arterial catheterization were performed. Arterial blood pressure was monitored and maintained at a mean of 90 to 120 mm Hg. Electrocardiogram was continuously monitored. The animal was placed on a water circulating heating pad in order to maintain rectal temperature at 37.5° C. To minimize respiratory movements, which make single-fiber recordings difficult, bilateral pneumothorax was performed and a paralyzing agent (Syncurine) was administered intravenously. The animal was ventilated with a positive-pressure respirator at 17 to 20 strokes per minute.

A pure cutaneous afferent nerve, the superficial radial nerve, was prepared for placement of stimulating and recording electrodes by carefully freeing a 10- to 15-mm segment from surrounding tissue near the wrist, and another proximal segment just above the elbow. Three pairs of Ag-AgCl hook electrodes, each imbedded in a plastic platform, were placed as follows: one pair of stimulating electrodes

was placed most distally under the exposed nerve, another pair for repetitive stimulation was placed approximately 15 mm proximal to the first pair, and a pair for recording compound action potentials was placed at the upper arm site (Fig. 1). The nerve conduction distance was 50 to 80 mm, allowing for adequate time separation of the recorded compound action potential components. The exposed nerve sites were then covered with a thin layer of agar made with Ringer's solution to minimize drying and heat loss. Small thermistor beads were placed at the electrode sites so that nerve temperature could be monitored and maintained at 36° to 38° C with small heat lamps.

Single-fiber action potentials were recorded through high impedance (10 to 60 mOhm) glass micropipettes filled with 3 M KCl. The microelectrodes were driven through the nerve at the site of the proximal recording platform by a Trent Wells hydraulic microdrive.* Signals from the microelectrodes were fed into a WPI electrometer and subsequently amplified by a Grass P511 preamplifier and fed into a Tektronix 565 oscilloscope for visual display and direct photographing with a Polaroid camera.† Compound action potentials were simultaneously recorded, displayed, and photographed from the oscilloscope screen.

Repetitive stimulation was delivered to the nerve by a commercial stimulator unit of the type used clinically.‡ This device is a radiofrequency, battery-powered unit that delivers 0.2-msec square waves of alternating polarity. Frequency can be varied from 6 to 200/sec and pulse intensity from 0 to 14 V (0 to 12 mA). The implantable portion of the unit is made of a Silastic cuff with imbedded platinum plates. Initially, we found it difficult to maintain adequate nerve/cuff stimulating-plate contact during the course of an experiment and wanted to eliminate possible depolarizing effects of the mechanical pressure of the cuff around the nerve. Therefore, we modified the stimulation by eliminating the Silastic cuff and substituting the pair of Ag-AgCl wires. The output of the neurostimulator unit was fed through the Ag wire electrodes, and the current at the nerve monitored through a separate circuit.

*Trent Wells hydraulic microdrive manufactured by Trent Wells, Inc., 8120 Otis Street, South Gate, California. WPI electrometer manufactured by W. P. Instruments, Inc., 60 Fitch Street, New Haven, Connecticut. Grass P511 preamplifier manufactured by Grass Instrument Company, 101 Old Colony Avenue, Quincy, Massachusetts. Tektronix 565 oscilloscope manufactured by Tektronix, Inc., Beaverton, Oregon.

†Polaroid camera manufactured by Polaroid Corp., Cambridge, Massachusetts.

‡Commercial stimulator unit manufactured by Avery Laboratories, Inc., Farmingdale, New York.

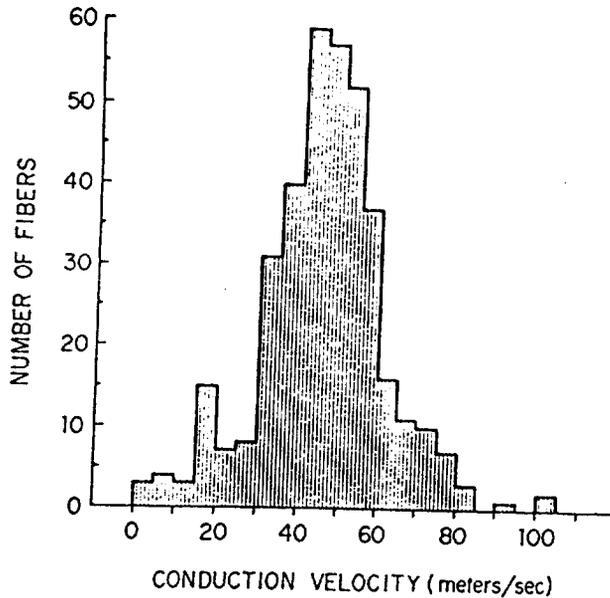


Fig. 2. Distribution of fiber conduction velocities for the 364 superficial radial nerve fibers sampled. Conduction velocities were determined from action potential latency to stimulation at threshold intensity for discharging the fiber.

The experimental procedure was to isolate a single fiber by driving the micropipette through the nerve at the proximal recording electrode platform while stimulating the nerve at the distal electrode site with single square wave pulses of 0.2 to 0.5 msec at supramaximal intensity for evoking a compound action potential (usually 4 to 10 × threshold) delivered by a Nuclear Chicago constant current stimulator[§] at a rate of 1/sec.

Once a fiber was isolated, stimulating current was reduced to threshold for discharging the fiber, and a photographic record was made of the fiber discharge and simultaneous nerve compound action potential. At the low rate of control stimulation (1/sec), threshold current intensity for a fiber did not vary. Control values of electrical threshold and conduction velocity (calculated from latency and conduction distance) for the fiber were noted. The test period consisted of first determining the electrical threshold of the fiber discharge to the repetitive stimulation unit (referred to as the neurostimulator). The nerve was

subsequently stimulated by the neurostimulator at fiber threshold intensity (usually one polarity of the alternating polarity pulses) at a rate of 180 to 200/sec for a period of 5 to 10 minutes. General observations were made on fiber discharge during repetitive stimulation, but systematic excitability testing was carried out upon termination of the repetitive stimulation, corresponding to the period of continuing clinical analgesia.

After the test period of repetitive stimulation, the threshold to single-pulse stimulation delivered by the Nuclear-Chicago stimulator was determined again, and the stimulus intensity and/or pulse width was adjusted as necessary. The fiber action potential and simultaneous compound action potential were photographed. Excitability changes observed were: conduction velocity, electrical threshold intensity, electrical threshold pulse width, and probability of discharge. If the threshold and/or conduction velocity differed from control prestimulation values, the time course of recovery to control values was followed as long as recording conditions permitted. In a few cases, testing was continued beyond the time of return to control values. After control conditions were re-established, another longer period of repetitive stimulation (10 to 20 minutes) at the neurostimulator threshold was applied, and post-stimulation threshold and conduction velocity determinations were made as described above. If fiber isolation was still maintained at this time, the neurostimulator current was adjusted to just below threshold for the fiber discharge to determine if excitability changes occur when the recorded fiber is not itself discharged. In a few cases, the skin receptive field for the fiber was determined, but the long recording time required for the above excitability testing usually precluded this natural sensitivity testing.

Results

Fiber Conduction Velocity Distribution

In 27 experiments 364 superficial radial nerve fibers were isolated and recorded long enough to make a control conduction velocity determination for each fiber. The conduction velocity was calculated from the latency of the fiber action potential to stimulation at threshold intensity for the fiber. The distribution of the fiber conduction velocities is shown in Fig. 2. This distribution resembles that published by others for data from superficial radial nerve fibers obtained in a similar manner.¹

Post-Stimulation Excitability Changes

Excitability following repetitive electrical stimulation was determined for 85 fibers. The remainder were driven by the repetitive stimulus, but were "lost" to the recording electrode before complete testing could

[§]Constant current stimulator manufactured by Nuclear Chicago, 2000 Nuclear Drive, Des Plaines, Illinois.

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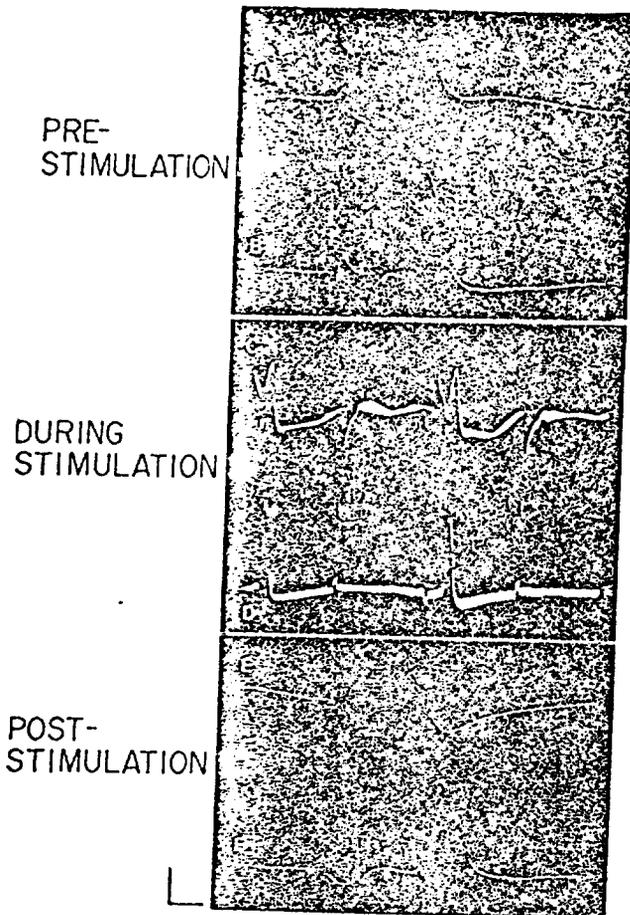


FIG. 3. Fiber conduction velocity change after repetitive electrical stimulation. A and B: Control recordings of compound action potential and single-fiber action potential, respectively, at threshold intensity for discharging the fiber (0.5 mA). Control conduction velocity was 51.4 m/sec. C and D: Records of the compound action potential and fiber action potential driven by the repetitive stimulus (182/sec) at threshold for driving the fiber at one polarity only. E and F: After 10 minutes of repetitive stimulation at these parameters, single-pulse stimulation at control threshold (as in A and B) evoked the compound action potential (E) and fiber action potential (F). The conduction velocity of the recorded fiber had decreased to 36 m/sec. Voltage calibration is 0.25 mV for A, C, and E, and 10 mV for B, D, and F. Time calibration is 0.5 msec for A, B, E, and F, and 2 msec for C and D. Conduction distance between distal control stimulating electrodes and recording micropipette was 54 mm.

be accomplished. Of those tested, 70 (82%) showed decreased excitability in one or more of the following forms: increased threshold current intensity, increased threshold stimulus pulse width, decreased probability of discharge, and/or decreased conduction velocity at threshold current. Of these 70 fibers, 66 had a conduction velocity greater than 30 m/sec, which classifies them as A-beta and A-gamma fibers. Four fibers had

a conduction velocity slower than 30 m/sec, in the A-delta range. No fibers in the C fiber range (conduction less than 1 m/sec) were included in this group.

Twenty-five of those fibers showing a decrease in excitability exhibited a slowing of conduction velocity with no change in electrical threshold. The mean conduction velocity for this group was 53.3 ± 17.0 m/sec.

Figure 3 shows the representative records from a fiber which underwent a slowing of conduction velocity following a period of repetitive stimulation (182/sec). The control conduction velocity was 51.4 m/sec before repetitive stimulation (Fig. 3 B). After the fiber was discharged at its threshold for driving by one polarity of the alternating polarity repetitive pulse train (Fig. 3 D), the threshold for discharging the fiber was unchanged, but the conduction velocity was decreased to 36 m/sec.

Both a conduction velocity change and a change in threshold parameters following repetitive stimulation were performed on 33 fibers. The mean conduction velocity for these fibers was 50.1 ± 11.7 m/sec. In Fig. 4 B, the control conduction velocity of the fiber was 51.9 m/sec, and the threshold intensity was 0.5 mA at a 0.14-msec pulse width. After 10 minutes of repetitive stimulation at one polarity, the threshold pulse width increased to 0.21 msec for a 0.5-mA pulse. Post-stimulation conduction velocity decreased slightly to 49.1 m/sec, and gradually returned to control values in 10 minutes. Figure 5 shows recordings for the same fiber subjected to higher intensity repetitive stimulation, sufficient to discharge the fiber at both stimulus polarities (Fig. 5 D). After this higher intensity stimulation, a longer threshold pulse width was required and a larger conduction velocity decrease, to 45 m/sec, was observed. The time course of recovery to control values was 30 minutes.

Figure 6 shows recordings for a fiber that underwent an increase in threshold following repetitive stimulation, but no change in conduction velocity was observed. This type of response was recorded for 12 fibers with a mean conduction velocity of 56.3 ± 9.6 m/sec. For the fiber recorded in Fig. 6, as for several others of the recorded sample, an unusual bursting pattern of discharge during repetitive stimulation was observed (Fig. 6 I). The fiber followed the stimulus pulse 1:1 for 50 msec, but ceased discharging for the next 100 msec, even though the 189/sec stimulation was continuous. The bursting periodicity was very regular throughout the repetitive stimulation and was not related to respiratory movements or to pulse rate.

The A beta-gamma fiber in Fig. 7 underwent an increased threshold following repetitive stimulation, from a control of 0.35 mA (Fig. 7 B), to a post-stimulation value of 0.45 mA (Fig. 7 D). The fiber threshold returned to the control value after 15 minutes (Fig. 7 F). However, this fiber displayed an apparent increase in conduction velocity when the increased threshold current was applied (Fig. 7 D). This

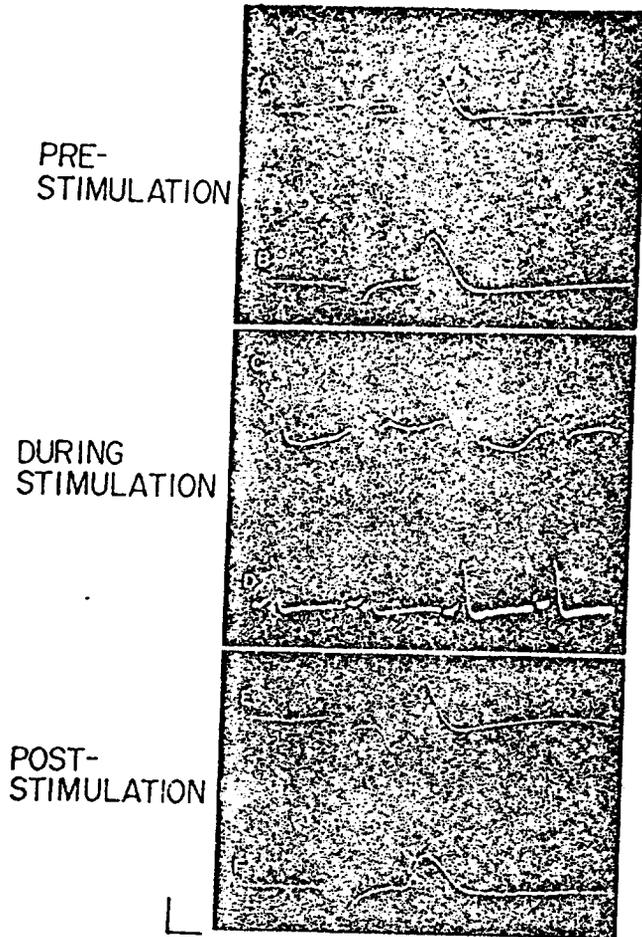


FIG. 4. Decrease in fiber conduction velocity and increase in threshold stimulus pulse width following repetitive stimulation. A and B: Control compound action potential (A) and fiber action potential (B) are shown at threshold for discharging the fiber (0.5 mA, 0.14 msec pulse width). Control conduction velocity of the fiber was 51.9 m/sec. B and C: Records of the compound action potential and fiber action potential evoked by the 182/sec repetitive stimulus at threshold levels for driving the fiber at one polarity. E and F: After 10 minutes of repetitive stimulation, the stimulus pulse width required to discharge the fiber at 0.5 mA is 0.21 msec (F). At these stimulus parameters, fiber conduction velocity had slightly decreased to 49.1 m/sec. The simultaneously recorded compound action potential is shown in E. Fiber conduction velocity and stimulus pulse width returned to control values in 10 minutes. Voltage calibration is 0.25 mV for A, C, and E, and 10 mV for B, D, and F. Time calibration is 0.5 msec for A, B, E, and F, and 2 msec for C and D. Conduction distance was 54 mm.

increased conduction velocity persisted for 15 minutes at which time the threshold current had returned to control values (Fig. 7 F). This fiber also showed a bursting response pattern during continuous repetitive (182/sec) stimulation (Fig. 7 I). Discharge bursts of 250 to 300 msec were separated by nondischarge intervals of 900 msec.

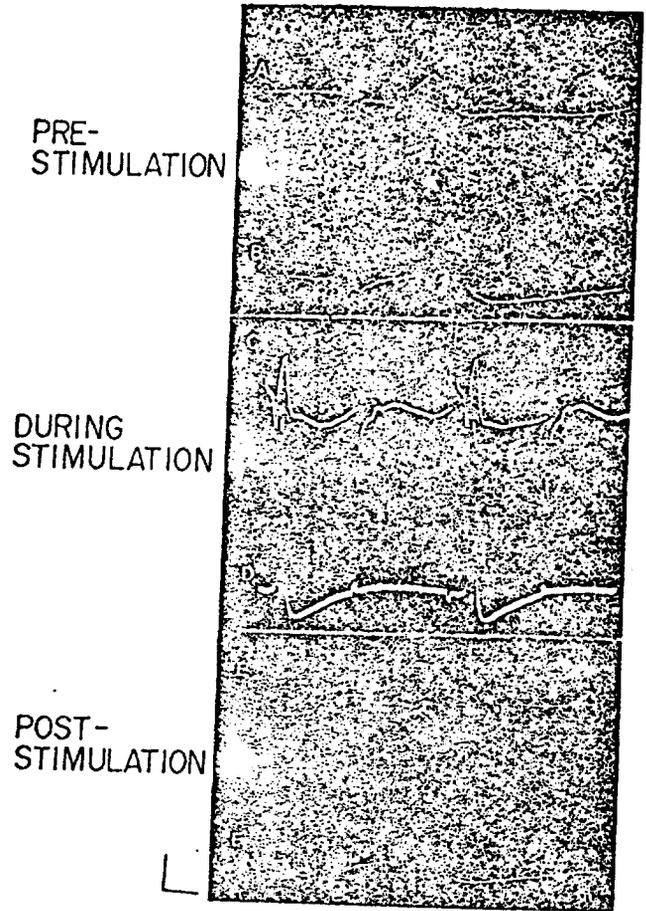


FIG. 5. Decrease in fiber conduction velocity and increase in threshold stimulus pulse width following repetitive stimulation. Same fiber as in Fig. 4 A and B: threshold for discharging the fiber was 0.5 mA, and pulse width 0.13 msec (B). Control conduction velocity was 54.0 m/sec. A shows the simultaneously recorded compound action potential. C and D: The compound action potential and fiber action potential driven by 182/sec repetitive stimulation at an intensity sufficient to discharge the fiber at both polarities. After 10 minutes of repetitive stimulation, the stimulus required to discharge the fiber was 0.5 mA and 0.25 msec pulse width. Conduction velocity was reduced to 45 m/sec. Recovery to control threshold stimulus parameters took 30 minutes. Voltage and time calibrations same as for Fig. 4.

For five fibers, recordings after repetitive stimulation revealed a decreased electrical threshold, suggesting an increased excitability. These five fibers had a mean conduction velocity of 54.5 m/sec.

The remaining 10 fibers tested either underwent no change or showed equivocal responses following repetitive stimulation. Of these fibers, two had a con-

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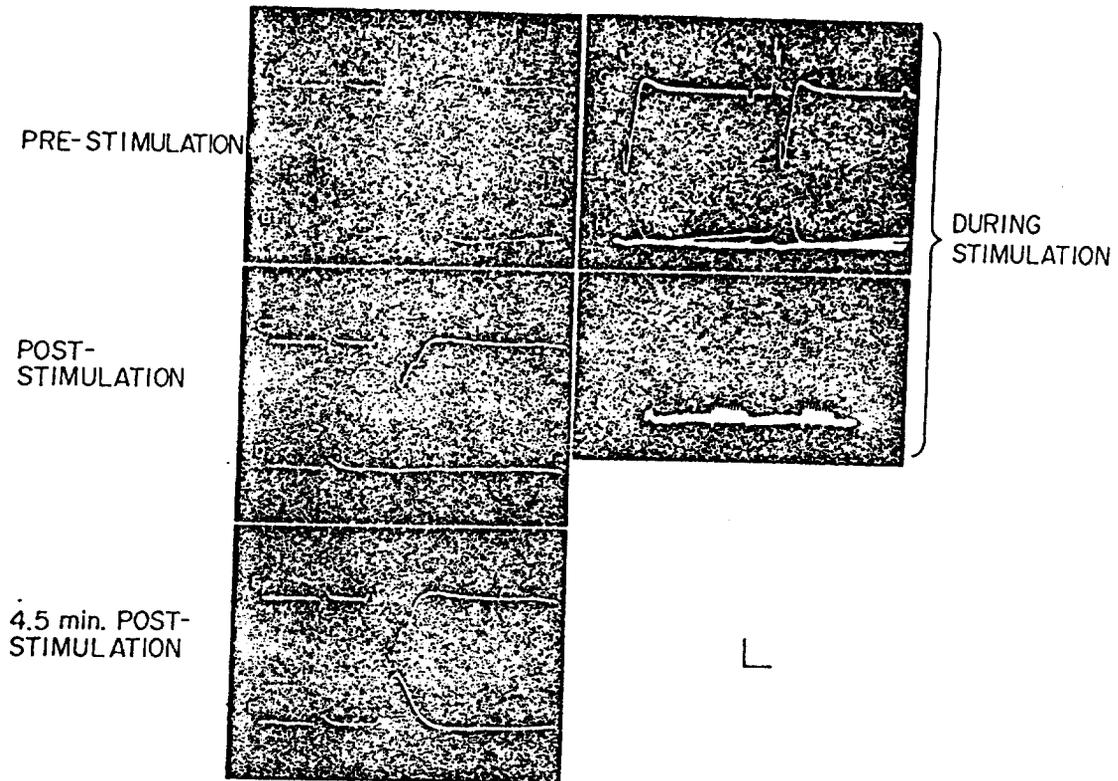


FIG. 6. Increased fiber threshold after repetitive stimulation. A and B: The control compound action potential and fiber action potential at fiber threshold (0.75 mA). Fiber conduction velocity was calculated to be 56.2 m/sec. G and H: Compound action potential and fiber action potential during repetitive (189/sec) stimulation of the nerve at threshold for driving the fiber at both stimulus polarities respectively. I: At slower sweep speed during repetitive stimulation, a fiber bursting pattern was observed. A 50 msec burst of nine to ten spikes/burst was followed by an "off" period lasting 100 to 110 msec. C and D: After 5 minutes of repetitive stimulation, the fiber was not driven at control threshold stimulus intensity (D); the simultaneous compound action potential in C shows a poststimulation decrease in amplitude. E and F: By 4.5 minutes after repetitive stimulation the threshold was still elevated for evoking the fiber (0.80 mA); the conduction velocity was unchanged at 56.2 m/sec (F). The compound action potential in E resembled that in A. Fiber threshold returned to control value by 10 minutes. Voltage calibration is 0.5 mV in A, C, E, and G, and 10 mV in B, D, F, H, and I. Time calibration is 0.5 msec in A-F, 1 msec in G and H, and 50 msec in I. Conduction distance was 59 mm.

duction velocity in the A-delta range. The mean conduction velocity for this group was 38.8 ± 14.1 m/sec.

Time Course of Excitability Change After Repetitive Stimulation

The return of fiber excitability to control, pre-stimulation values of conduction velocity and/or threshold, followed a time course dependent on current intensity of the repetitive stimulus and on the duration of the repetitive train. For a 5-minute period of repetitive stimulation at threshold levels (usually one stimulus polarity evoked the fiber action potential), the average time of recovery to control was 11 minutes. Higher intensity stimulation or a longer period of repetitive stimulation resulted in a longer

time course of recovery. The time course appeared to be similar for fibers showing decreased and increased excitability.

An unexpected finding was that five fibers (mean conduction velocity 48 m/sec) showed the common pattern of decreased excitability immediately following repetitive stimulation with a time course of return to control values of 10 to 20 minutes. If the fibers were recorded beyond the time of return to control, however, a period of enhanced excitability was observed. Figure 8 shows the records for such a fiber. In A, the control threshold was 0.52 mA and conduction velocity was 42.7 m/sec. In B, the fiber was driven intermittently at threshold by the repetitive stimulus (182/sec) for 5 minutes. Immediately after

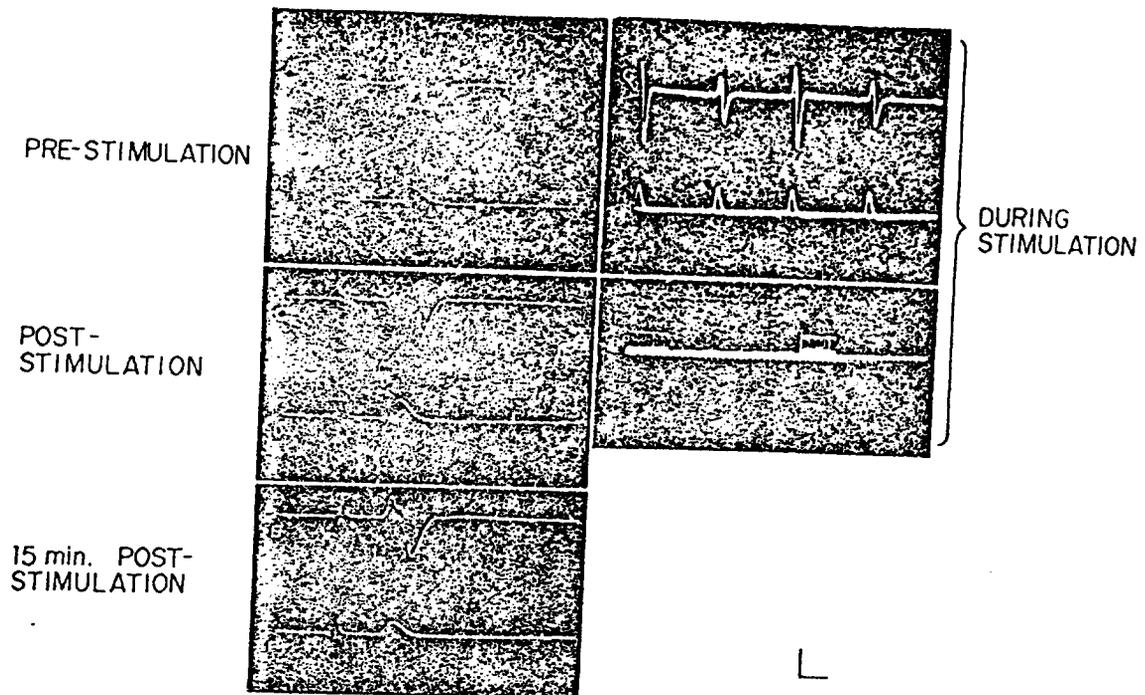


FIG. 7. Increased fiber threshold following repetitive stimulation. A and B: The compound action potential and the fiber action potential at fiber threshold (0.35 mA). Fiber conduction velocity was calculated to be 65.6 m/sec. G, H, and I: Records photographed during 182/sec repetitive stimulation at threshold for discharging the fiber at both stimulus polarities. G shows the compound action potential, and H and I show the fiber discharge at two different sweep speeds. In I, a bursting pattern was observed. The fiber followed stimulation for 250 to 300 msec, but was not discharged for an interval of 880 to 900 msec. C (compound action potential) and D (fiber action potential): Records photographed immediately after 5 minutes of repetitive stimulation. New threshold stimulus intensity was 0.45 mA.; fiber conduction velocity increased to 68.6 m/sec. E and F: Fifteen minutes after cessation of repetitive stimulation, fiber threshold returned to control, but conduction velocity remained elevated at 68.6 m/sec. Voltage calibration in A, C, E, and G is 0.5 mV, and 10 mV in B, D, F, H, and I. Time calibration is 0.5 msec in A-F, 2 msec in G and H, and 200 msec in I. Conduction distance was 59 mm.

repetitive stimulation, the threshold required for discharge was 0.60 mA (Fig. 8 C). Figure 9 shows the time course of recovery of excitability for the same fiber. This fiber was tested for 17 minutes following termination of the repetitive train, and was then lost to the recording electrode. It can be seen that the elevated threshold returns to control value by 6 minutes, but decreased thereafter.

It is possible that more fibers undergo this kind of decreased/increased excitability pattern, but most fibers were not recorded beyond return to control value.

Discharge During Repetitive Stimulation

The repetitive stimulator unit delivers square waves of alternating polarity, so that at threshold levels for driving the fiber, an action potential was recorded 1:2. That is, for every other pulse, presumably when the cathode was nearest the recording electrode, an action potential was evoked. This means that if the repetitive

frequency was 200/sec at just threshold for driving by one stimulus polarity, the actual repetitive frequency was 100/sec. Some fibers followed faithfully 1:2; most showed intermittent discharge at just threshold. A slight increase in the repetitive stimulus intensity caused the fiber to be driven at both polarities of stimulation (see Fig. 5). At this intensity, usually one polarity (when the cathode was nearest to the recording electrode) showed 1:1 frequency following, whereas the other polarity (anode nearest) showed intermittent frequency following. Many fibers would follow 1:1 or 1:2 repetitive stimulation for 2 to 3 minutes of the repetitive train, and then the probability of discharge would decrease.

Spontaneous Firing Following Repetitive Stimulation

Although no recorded fibers displayed a resting "spontaneous" discharge, six showed discharge in the absence of intentional stimulation following a trial of repetitive stimulation at fiber threshold. This dis-

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charge was intermittent and irregular and occurred upon termination of the repetitive train. The mean conduction velocity of these six fibers was 57 m/sec.

Excitability Changes in Fibers Not Driven by Repetitive Stimulation

In three fibers an excitability change was detected after repetitive stimulation below the threshold level for discharging the recorded fiber. These fibers were tested initially for their responses to repetitive stimulation above threshold, and all three showed the commonly observed transient threshold increase (decreased excitability) after termination of the repetitive train. When these fibers were subjected to repetitive stimulation below fiber threshold, a decrease in threshold (increased excitability) upon termination of the repetitive train was observed. Generally, the decrease in threshold elicited by stimulation below threshold levels was less pronounced than the increase in threshold elicited by stimulation above threshold levels.

Discussion

Of the fibers in the superficial radial nerve sample tested for responses to repetitive electrical stimulation, 88% underwent an excitability change upon termination of the repetitive stimulation. The predominant change (82%) was a decreased excitability manifested as a transient decrease in conduction velocity and/or increase in electrical threshold for discharge. The radial nerve was left intact in these experiments in order to maintain normal physiological conditions for the 8- to 12-hour recording period. It is possible that central mechanisms, such as post-tetanic polarization of afferent terminals and descending pathways, might be contributing to the peripheral nerve excitability changes, in addition to changes occurring peripherally. An afferent volley produces a DRP (dorsal root potential) that electrotonically spreads along the primary afferent fibers, the spatial decrement depending on fiber diameter. An afferent volley can also produce PAD (primary afferent depolarization) in a myelinated fiber, even if that fiber is not activated by the stimulus. The question is raised whether the PAD spreads distally from the spinal cord as far as our recording site (120 mm) in the intact preparation. Jänig and Zimmerman⁷ reported that at 8 mm from the cord, the A fiber DRP's decayed to 25 μ V and C fiber DRP's to 6 μ V. Thus, it does not seem likely that the fiber excitability changes we recorded are confounded by these electronic, antidromic potentials.

Another type of peripheral nerve fiber interaction or coupling has been reported by Matthews.¹² His findings in the saphenous nerve of cats suggest that an impulse propagated toward the terminals of one afferent nerve may generate an orthodromic impulse in another. However, it was not reported whether this phenomenon occurs under conditions of repetitive stimulation. Such a mechanism could explain the ex-

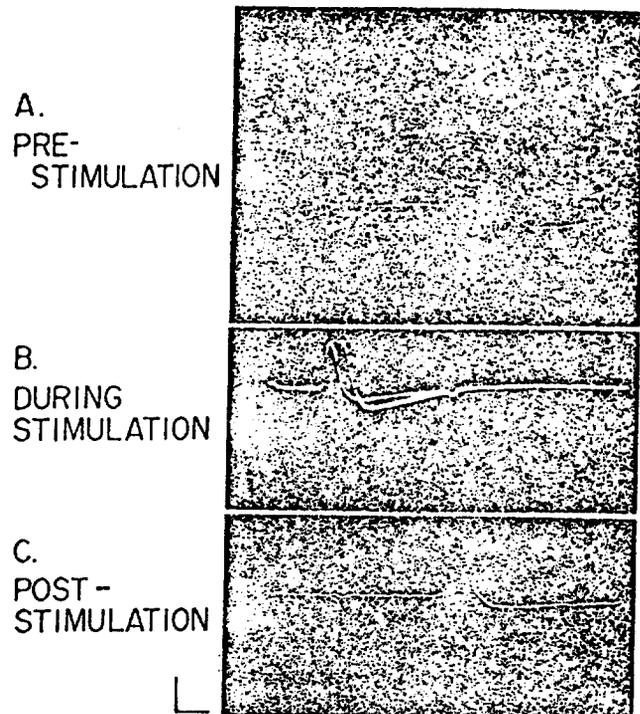


FIG. 8. Increased fiber threshold following repetitive stimulation. A: Control threshold for discharging the fiber was 0.52 mA; conduction velocity was calculated to be 42.7 m/sec. B: Repetitive stimulation, 182/sec, at threshold for driving the fiber at one polarity was applied for 5 minutes. C: Immediately following repetitive stimulation, fiber threshold was increased to 0.60 mA; conduction velocity remained at 42.7 m/sec. Voltage calibration is 2.5 mV. Time calibration is 0.5 msec for A and C, 1 msec for B. Conduction distance was 67 mm.

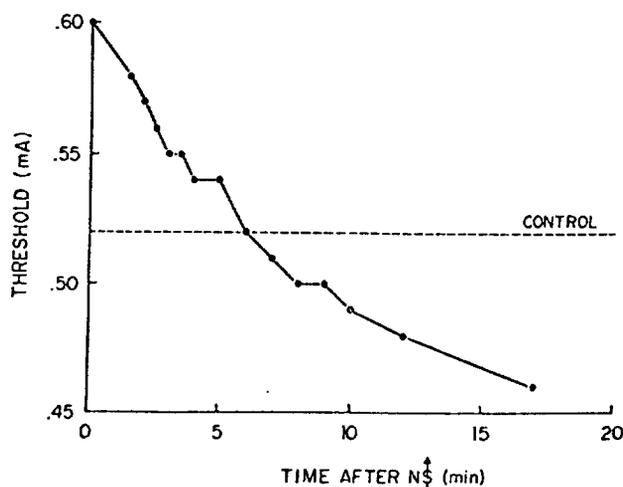


FIG. 9. Time course of fiber excitability change after repetitive stimulation. Points represent times after repetitive stimulation at which fiber threshold was tested for the fiber in Fig. 8. Dotted line represents control, prestimulation threshold. Control threshold was reached at 6 minutes after repetitive stimulation. Fiber was recorded for 17 minutes.

citability changes we observed in fibers subjected to repetitive stimulation at intensities below threshold for discharging the fiber.

In our tested sample, fibers of large and small diameters appear to undergo similar excitability changes, although few fibers in the A-delta range were studied. If the majority of all peripheral nerve fibers decreases in excitability peripherally in response to high-frequency repetitive stimulation, suggesting hyperpolarization, then subsequent orthodromic activity in these fibers would be reduced until normal excitability is restored. The same high-frequency stimulation produces hyperpolarization in the primary afferent fibers of the discharged fibers,^{17,23,25} and this polarization results in post-tetanic, postsynaptic facilitation due to a larger amplitude presynaptic afferent terminal action potential. The same stimulation also produces PAD in some terminals, as mentioned above. This PAD results in reduced afferent flow into the spinal cord. However, it is unlikely that PAD follows the high frequency of stimulation used in these experiments. If, as we have proposed, there is a peripheral blocking effect (such as hyperpolarization) produced by repetitive stimulation, it would have the effect of preventing the hyperpolarization and/or depolarization from occurring at the primary afferent terminals in the cord. In terms of pain modulation, this suggests a rather unselective blocking of large-fiber afferent inflow by high-frequency repetitive stimulation, the magnitude of the block being dependent on the intensity and the duration of repetitive stimulation. Such a depression of large-fiber input is not consistent with the Melzack-Wall hypothesis,¹³ in which suppression of small-fiber nociceptive input is mediated by large-fiber activity. If the large-fiber activity itself is suppressed by repetitive stimulation, its ability to inhibit nociceptive input at the spinal cord would be reduced. Although only four fibers in the sample were in the A-delta range, the changes in excitability following repetitive electrical stimulation resembled those for the larger diameters fibers, suggesting that fibers of all sizes may undergo similar excitability changes. We are currently investigating that aspect further.

The effect of changing the repetitive frequency has not as yet been tested by us. It has been suggested by Eriksson and Sjölund³ that low frequencies (1 to 2 Hz) of high-intensity transcutaneous electrical stimulation provide pain relief by activation central inhibitory mechanisms, such as the brain-stem endorphin system. A possible hypothesis is that high-frequency stimulation reduces afferent input by a peripheral mechanism, whereas low-frequency stimulation activates central systems that modulate pain.

The five fibers that showed an initially decreased excitability followed by an enhanced excitability were all larger than the A-delta range. If fibers carrying nociceptive information also undergo these changes after repetitive stimulation, they may have their

clinical correlate in the reports from many patients that, after the analgesia which persists when repetitive electrical stimulation is terminated, the pain returns with greater intensity (unpublished observations).

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