Peripheral nerve stimulation suppression of C-fiber-evoked flexion reflex in rats

Part 1: Parameters of continuous stimulation

BENGT H. SJÖLUND, M.D., PH.D.

Science Branch, Medical Board of the Armed Forces, Karolinen, Karlstad, Sweden

Transcutaneous electrical nerve stimulation (TENS) is now a well established clinical technique to alleviate chronic pain. Its mechanism of action remains unknown and the stimulation parameters used are based on subjective reports from patients. In the present study, a systematic investigation has been performed with conditioning stimulation of different parameters delivered to a dissected skin nerve in the lightly anesthetized rat, utilizing the size of a C-fiber-evoked flexion reflex as a measure of transmission from nociceptive afferent fibers in the spinal cord. A stimulation intensity that recruited both A-beta and A-delta fibers was more effective in depressing the C-fiber-evoked reflex at all frequencies studied than were intensities activating A-beta fibers only. A stimulation frequency of 80 Hz gave the most profound inhibition. The implications for clinical treatment are discussed.

KEY WORDS • transcutaneous electrical nerve stimulation • C-fiber • pain • peripheral nerve stimulation • reflex suppression • rat

For more than a decade, transcutaneous electrical nerve stimulation (TENS) has been used for the alleviation of chronic pain. With the original technique (conventional TENS), mainly superficial nerve fibers are stimulated at 10 to 120 Hz at an intensity evoking a tingling sensation in the painful region. It has been hypothesized that this stimulation closes a "gate" to nociceptive information entering the human spinal cord. It is well known that various afferent nerves may mutually inhibit each other at a presynaptic level. It may therefore be that such mechanisms are at least partly responsible for the effects observed; however, the optimal parameters for producing presynaptic and other forms of long-standing inhibition of afferent impulse in man are not well defined. Only subjective reports of what feels "pleasant" or is preferred by small numbers of patients undergoing TENS have been published.

The reason for the present study was to undertake a systematic investigation in a mammal of the most suitable parameters for conditioning stimulation of a skin nerve to elicit maximal suppression of a C-fiber-evoked flexion reflex in a nearby spinal segment.

Materials and Methods

Eighty-two Wistar rats, weighing 250 to 300 gm each, were used for the present study. The method of preparation has been described elsewhere. Briefly, the rats were anesthetized with 1% to 1.5% halothane in a moist nitrous oxide/oxygen mixture (2:1). A tracheostomy was made, and one external jugular vein and one carotid artery were cannulated. In one hindlimb, the plantar and sural nerves were dissected for stimulation and the common peroneal and sciatic nerves were exposed for flexion reflex and nerve volley recordings, respectively (Fig. 1).

During nerve measurements the animals were paralyzed with gallamine and artificially ventilated. The halothane concentration was lowered to 0.4%, still allowing stable anesthesia with constricted pupils and no blood pressure variations. Blood pressure, end-expiratory CO2 concentration, and rectal temperature were monitored continuously and kept at 120 to 140 mm Hg, 3.5% to 4%, and 37° to 38.5°C, respectively. The reflex discharges elicited by stimulation with five shocks at 10-msec intervals were recorded from two poles as
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were monophasic square waves of 150-msec duration. Preparations where the dissected nerves had a threshold of more than 20 μAmp were discarded.

Results

As can be seen in Fig. 2A to H, a short-latency flexion reflex can be evoked in the common peroneal nerve by stimulation at twice threshold; that is, at a strength recruiting only A-beta fibers (compare Lloyd⁹). An additional long-latency discharge is evoked only at a stimulation strength recruiting C-fibers (Fig. 2I to L). This discharge has properties similar to that of a subgroup of Class 2 neurons in the dorsal horn,¹³,¹⁶ and is very sensitive to morphine in the cat.⁷ The relationship between the raw data (lower sweeps) and their integers (upper sweeps) is illustrated in Fig. 21 to L.

The results from a typical experiment with conditioning stimulation are illustrated in Fig. 3. The ipsilateral plantar nerve was stimulated at 100 times threshold at the intervals indicated. Between B and C, the ipsilateral sural nerve was stimulated with a frequency of 40 Hz at 10 times threshold for 30 minutes. It can be seen that after this conditioning stimulation there is a transient (C to E) decrease of the C-fiber-evoked discharge, which returned to the control level 75 minutes after the end of the conditioning stimulation.

Figure 4 summarizes the results from all the rats at the two stimulation intensities (twice and 10 times threshold) and the seven stimulation frequencies (10,
FIG. 3. Results of a typical experiment with ipsilateral plantar nerve stimulation 100 times threshold (iPlant. 100T), and a conditioning stimulation of ipsilateral sural nerve at 40 Hz (10 times threshold) for 30 minutes between B and C (arrow). Numbers denote time from start (control) in minutes. Recordings are from the ipsilateral common peroneal nerve (iPer.). Int. = rectified and integrated responses.

40, 60, 80, 100, 120, and 160 Hz) tested. Each combination was tested in at least five rats and, after normalization to 100% of reflex control values (stable and measured at least twice with an interval of 15 minutes), the mean amplitude of the integrated reflex response is given at the times indicated. It can be seen that, with a weak intensity (twice threshold, A–D and I–K), 10, 40, 60, and 160 Hz caused no significant depression of the reflex discharge. On the other hand, stimulation at 80 and 100 Hz resulted in marked long-lasting depressions of the C-fiber-evoked reflex. With higher stimulus intensity (10 times threshold, E–H and L–N), only stimulation at 10 Hz caused no significant depression, whereas the other frequencies depressed the reflex discharges to a varying extent. Stimulation at 40 to 80 Hz, however, had a more marked effect than the other frequencies tested.

Discussion

The results in this study show that a C-fiber-evoked flexion reflex in the rat is susceptible to a 30-minute conditioning stimulation of afferent fibers in an ipsilateral cutaneous nerve adjacent to that used for eliciting the reflex.

The reflex depression elicited has a time course similar to the pain relief seen after TENS in man, and indicates a temporary decrease of the transmission from nociceptive C-fibers to second-order neurons in the spinal cord of this mammal. The corresponding flexion reflex in the spinal cord-transected cat has previously been shown to be sensitive to morphine and to low-frequency conditioning stimulation of Group II and III afferent muscle fibers.

This study also indicates that a higher stimulus intensity (at 10 times threshold), recruiting A-delta fibers in addition to the A-beta fibers, gives a more efficient suppression of the transmission of nociceptive stimuli than does stimulation at a lower intensity (twice threshold), which activates only A-beta fibers. Moreover, a weak stimulus intensity seems to make the choice of stimulus frequency more critical in that only 80- to 100-Hz stimulation caused a marked reflex depression with this intensity. With higher stimulus intensity, on the other hand, stimulus frequencies in the range of 40 to 160 Hz all gave a significant depression of the reflex discharge.

The depression of the C-fiber-evoked flexion reflex in this mammal by long-lasting conditioning stimulation of skin afferent fibers in a nerve adjacent to that used to elicit the reflex may well have a relationship to the pain relief enjoyed by man after TENS. If so, these results speak against a peripheral fatigue phenomenon as the sole cause of such pain relief; instead they stress the importance of selection of proper stimulus parameters for TENS in man. Thus, the highest tolerable stimulus intensity should be used, since marked A-delta fiber stimulation causes an unpleasant pinprick sensation, and the stimulation frequency should not be less than 40 Hz. If a weaker stimulation is used, the frequency may ideally be around 80 Hz, since there is nothing to indicate a markedly different time course of inhibitory phenomena in the spinal cord from mammal to mammal. A double-blind study in patients with chronic facial pain is in progress in an effort to confirm the application of these findings to man.

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References

3. Eccles RM, Lundberg A: Synaptic actions in motoneurones by afferents which may evoke the flexion reflex. Arch Ital Biol 97:199–221, 1959
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Fig. 4. Summary of all experiments. Controls in each rat normalized to 100%. Each dot is the mean amplitude (± standard error of the mean (SEM)) of the number of rats given (n). C = control; A = after conditioning stimulation (interrupted bar); T = threshold.

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Address reprint requests to: Bengt H. Sjölund, M.D., Ph.D., Science Branch, Medical Board of the Armed Forces, Karolinen, S-651 80 Karlstad, Sweden.