Inhibition of primate spinothalamic tract cells by TENS

KYU HO LEE, M.D., JIN MO CHUNG, PH.D., AND WILLIAM D. WILLIS, JR., M.D., PH.D.
Marine Biomedical Institute and Departments of Anatomy and Physiology and Biophysics, University of endogenous opioid substances.

Transcutaneous electrical nerve stimulation (TENS) was applied in an experimental animal model to investigate the underlying mechanisms of this treatment. Recordings were made from identified spinothalamic tract (STT) neurons in the lumbosacral spinal cords of seven anesthetized monkeys. The STT cells were activated by stimulating the common peroneal nerve at a suprathreshold intensity for C-fibers. Evoked responses of C-fibers were compared before, during, and after application of TENS for 5 minutes from a commercially available TENS unit. The current delivered by the TENS unit was monitored.

In 14 STT cells, some degree of inhibition of C-fiber evoked responses occurred only when the intensity of TENS exceeded the threshold of Aδ fibers. At a given stimulus intensity, bursts of pulses repeated at a low rate were more effective than high-rate pulses. When TENS was applied to an area of the skin within a cell’s receptive field, it was more effective than when it was applied outside the receptive field. The C-fiber volley recorded from a peripheral nerve was not reduced in size, and there were no substantial changes in its latency due to TENS. The inhibition of the activity of STT cells was not altered appreciably after intravenous injection of naloxone hydrochloride.

These results suggest that TENS produces central nervous system inhibition by activating Aδ afferent fibers. The inhibitory effects of TENS on STT cells appear to be due to a mechanism that does not involve release of endogenous opioid substances.

KEY WORDS: transcutaneous electrical nerve stimulation • analgesia • afferent nerve stimulation • spinothalamic tract cells • primate • endogenous opioids

Transcutaneous electrical nerve stimulation (TENS), acupuncture-needling, and electroacupuncture are useful non-ablative methods for relief of acute and chronic pain in medical practice. These procedures appear to work by causing an increased discharge in afferent nerve fibers which in turn modifies the transmission of impulses in pain pathways. Many reports have described the analgesic effect of afferent nerve stimulation. There are also numerous studies concerning the mechanisms responsible for the analgesia produced by afferent nerve stimulation.

A plausible explanation of the effects of afferent nerve stimulation originates from the gate control theory, which focuses on segmental spinal inhibitory mechanisms. Although some evidence in support of a spinal mechanism has been accumulated, the results from psychophysical experiments in humans are partly contradictory. At the present, the specific mechanisms involved in analgesia produced by peripheral nerve stimulation are controversial.

One of the well known nociceptive second-order neuronal pathways in the spinal cord, the spinothalamic tract (STT), is thought to be the main sensory tract concerned with pain sensations originating from the body and viscera in humans. The STT is likely to have a similar role in subhuman primates. The responses of STT cells to graded intensities of noxious mechanical or thermal stimuli applied to the skin are appropriate for participation of these neurons in nociception. Many of them have a convergent input from skin, muscle, and/or viscera, and so may be involved in the phenomenon of pain referral. Analgesic manipulations inhibit the activity of STT cells in primates. Although there are many measures of analgesia, such as a diminution in various manifestations of the flexor withdrawal reflex, we believe that it is useful for the study of pain mechanisms to determine what changes are produced in the activity of STT cells by nociceptive and anti-nociceptive procedures in animals, since STT cells may more accurately reflect sensory events than do reflex changes.
TENS inhibition of primate spinothalamic cells

FIG. 1. An example of the responses of a wide dynamic range spinothalamic tract (STT) cell. In these figures “Events” indicates the number of neural impulses/bin. A: Location of the stimulating electrode. VPLc = caudal part of the ventral posterior lateral nucleus; VPM = ventral posterior medial nucleus; R = reticular nucleus; LP = lateral posterior nucleus; GLD = dorsal nucleus of the lateral geniculate body. B: Location of the STT cell. C: The receptive field (cross-hatched area) and responses to graded mechanical stimulation in the receptive field. D: The antidromic response of the cell to electrical stimulation in the thalamus. E: Orthodromic and antidromic spikes. F: Collision between orthodromic and antidromic action potentials. Arrows indicate shock artifacts in the tracings.

Provided that inhibition of the activity of STT cells is a correlate of analgesia, a direct measurement of inhibition of STT cells could help us to understand the mechanisms underlying the clinical effects of TENS, as well as of acupuncture. The results of our previous study showing that peripheral nerve stimulation induces inhibition of STT cells in primates have encouraged us to try a commercially available TENS unit that delivers electric currents through carbon rubber surface electrodes on the skin instead of direct stimulation of peripheral nerves.

By observation of the activity of STT cells during and after TENS in our animal model, we have investigated possible analgesic mechanisms and also several factors influencing the effectiveness of TENS. A preliminary report has been made in abstract form.

Materials and Methods

Seven monkeys (Macaca fascicularis) of either sex, each weighing 2 to 3.5 kg, were used in this study. Anesthesia was initially induced in each animal with a mixture of oxygen, nitrous oxide, and halothane; then the gas anesthesia was discontinued, and a single intravenous injection of alpha-chloralose (60 mg/kg) was given. A supplemental infusion of sodium pentobarbital (4 mg/kg/hr) was used to maintain a proper anesthetic level, and intravenous gallamine triethiodide (4 mg/kg/hr) was given continuously to immobilize the animal. Respiration was maintained artificially, and end-tidal CO₂ was kept at a level of 3.5% to 4.5%. Rectal temperature was regulated near 37°C.

A laminectomy exposed the lumbosacral spinal cord for microelectrode tracking in search of STT cells in the dorsal horn. A craniectomy at the vertex of the frontoparietal region of the skull provided an approach to the thalamus. The monkey was placed in a stereotaxic frame. Peripheral nerves, including the sural, common peroneal, and tibial nerves, were carefully dissected from the surrounding connective tissue, and were placed on pairs of stimulating electrodes. A pair of recording electrodes was placed on the sural nerve proximal to the stimulating electrodes at a suitable distance (3 to 5 cm), to record compound action potentials. The nerves were covered by a pool of warm mineral oil.

The caudal part of the ventral posterior lateral nucleus (VPLc) of the contralateral thalamus was found by recording potentials evoked by electrical stimulation of the dorsal column and by mechanical stimulation of the hindlimb. The thalamic electrode was then used to activate STT cells antidromically. Extracellular recordings were made with carbon-fiber microelectrodes (impedances of 2 to 4 Mohm) in the lumbosacral spinal cord segment showing the largest negative cord dorsum potential elicited by stimulation of the common peroneal nerve. Once STT cells were identified using the criteria of constant latency, ability to follow high rates of stimulation, and collision of antidromic action potentials with orthodromic spikes, the excitatory receptive fields were mapped, and STT cells were classified according to their responses to innocuous or noxious mechanical stimuli applied to the receptive fields as shown in Fig. 1. Then TENS surface electrodes (carbon rubber,
K. H. Lee, J. M. Chung and W. D. Willis, Jr.

Fig. 2. Responses of a spinothalamic tract cell evoked by test stimuli applied to the common peroneal nerve and effects of transcutaneous electrical nerve stimulation (TENS, at 2.5 x the cord dorsum N3 wave threshold, low-rate "comfort bursts"). A: A single-pass peri-stimulus time histogram that shows all of the activity of the cell induced by test stimuli and by TENS. Note that TENS activates the cell. B: The summed responses of the cell to 10 consecutive test stimuli applied to the common peroneal nerve with an intensity that was suprathreshold for C-fibers. During the period indicated by the bracket, C-fiber evoked responses (C-Resp.) could be counted separately for statistical comparisons. Alternatively, the complete responses to A- and C-fibers could be counted. C: Inhibition of the responses to A- and C-fibers by TENS. D: Inhibition of the responses to C-fibers alone. Brackets in A, C, and D indicate the time of TENS application.

1.5 x 1.75 in.) were placed in contact with the skin of the hindlimb in a region in which the hair had been clipped. The proximal electrode had a negative polarity. Isolated single-unit spikes were amplified and used to trigger window discriminator pulses, which were then led to a digital computer for compilation of peristimulus time histograms. The responses of STT cells evoked by common peroneal nerve stimulation were used as a test for TENS inhibition. These included discharges evoked by A-fiber and C-fiber volleys. The common peroneal nerve was stimulated with a train of three pulses (internal frequency, 30 Hz) at an intensity that was suprathreshold for C-fibers to maximize the activity evoked by the C-fibers. Stimulation was repeated every 10 seconds. Since TENS itself often activated STT cells, to avoid this interference we used a special stimulation paradigm. By means of a delay apparatus, TENS was applied between consecutive trains of test stimuli of the common peroneal nerve. Stimulation was applied for 7 to 9 seconds in every 10 seconds, and lasted for 5 minutes. Stimulus intensities delivered through TENS surface electrodes (impedances 1.0 to 3.0 kohm) were monitored and related to the cord dorsum potentials evoked by TENS. Both of the two types of TENS stimulus modes that were designed by the device manufacturer — high-frequency trains (85 Hz) and low-rate "comfort bursts" (3 bursts/sec, 7 pulses/burst, internal frequency 85 Hz) — were used at a fixed pulse width of 80 μsec. The reason why we used 5 minutes for conditioning with TENS is that maximal TENS effects have been shown within that period. We monitored changes in STT cell activity for 150 seconds after termination of TENS because, after 5 minutes of TENS, the responses of STT cells had nearly recovered by 150 seconds. By using this short period of stimulation, we could repeat the test several times in a given experiment.

For some STT cells, noxious heat was applied as a test stimulus, using a Peltier thermode on the glabrous skin in the receptive field, instead of electrical stimulation of the common peroneal nerve.

At the end of each experiment, the stimulating and recording sites were marked by passing small amounts of direct current (+20 μA, 10 seconds, for each mark) through the electrodes. The electrode marks made by the steel electrodes in the thalamus were enhanced histologically by Prussian blue staining, and carbon-fiber electrode marks near STT cells in the dorsal horn were visible as microlesions.

Data are expressed as a percentage of the averaged control values because evoked responses varied from
TENS inhibition of primate spinothalamic cells

one TENS unit to another. Statistical comparisons were performed using the paired Student t-test. Two-tailed p values less than 0.05 were considered to be significant.

Results
The latencies of the antidromic action potentials of the 14 cells studied in the seven monkeys ranged from 3.0 to 8.8 msec, except for one that was 17.0 msec, implying that the axonal conduction velocities were appropriate for myelinated axons (12 to 67 m/sec). Unexpectedly, all of the cells in the sample were wide dynamic range cells. These wide dynamic range (or multireceptive) cells can be excited by innocuous mechanical stimulation of the skin, but they are more effectively excited by noxious mechanical stimuli. In other studies, a substantial fraction of the STT cell population could be classified as high-threshold (or nociceptive-specific) neurons, since the cells were excited only by noxious intensities of stimulation.15,23,37,60

Method of Analysis

Figure 2 shows an example of the activity of one STT cell during and after application of TENS to the receptive field. This cell responded in a characteristic pattern to a volley in the A- and C-fibers of the common peroneal nerve with early and late discharges, as shown in Fig. 2B. The histogram in Fig. 2A reveals the total activity of the cell when excited by test stimuli applied to the common peroneal nerve and by TENS. Test stimuli were given every 10 seconds, and these produced peaks of activity. The background activity can be seen between peak responses. After five test responses were recorded, TENS conditioning was begun and lasted for the period shown by the horizontal bracket above the histogram. In this case, the strength of the TENS shocks was at an intensity of 2.5 times the threshold for the N3 wave, which signifies activation of Aδ fibers,7 regardless of which train mode was used, TENS markedly inhibited the responses of the STT cell to C-fiber volleys both during and just after TENS application (Fig. 3D and F). Stimulation with an intensity below the N3 threshold (3 x threshold for the cord dorsum N1 wave, which probably activates just Aαβ fibers,7 did not produce inhibition, and there was no post-TENS effect (Fig. 3C and E). The inhibition produced by low-rate bursts of TENS developed progressively, reaching a maximum about 60 seconds from the beginning of TENS (Fig. 3D). The level of inhibition stayed relatively constant until TENS was terminated, and then the evoked responses returned gradually to the control level. The degree of inhibition was greater with the low-rate burst mode than with high-frequency TENS at the same intensity. However, high-frequency TENS produced an abrupt onset of inhibition (Fig. 3F), followed by a somewhat decreased inhibition until about 90 seconds after the start of TENS application, and then the inhibition continued at the same level until termination of TENS. The responses induced by the test stimuli generally returned rapidly to the control level, although in this example there was a prolonged but fluctuating inhibition in the period after TENS.

A total of 13 paired trials of low- and high-frequency TENS with intensities over the N3 threshold in 10 STT cells and four paired trials below the N3 threshold in four cells were recorded. For statistical comparisons, the responses were expressed as the mean percentage of control values averaged at 30-second intervals, as shown in Fig. 4. In 13 cases, both the low-rate burst mode and high-frequency TENS were used, one after the other, and the results were compared. Although the absolute intensities used were different from unit to unit (intensity ranges 1.3 to 4.3 x N3 threshold), the C-fiber responses of the STT cells were inhibited about 50% during the time of low-rate burst TENS application, but high-frequency TENS produced only 30% inhibition. The difference was significant (p < 0.001). Post-TENS inhibition of C-fiber responses was not different for low- and high-frequency TENS. The degree of inhibition decreased approximately exponentially, and
FIG. 3. Differences in inhibition by transcutaneous electrical nerve stimulation (TENS) according to stimulating parameters (intensity and frequency). A and B show superimposed oscilloscope tracings (five sweeps) of the cord dorsum potentials produced by pulses identical to those delivered by the TENS unit with an intensity of 3 times the threshold for the N1 wave (3 × TN1) in A and with an intensity of 3 times the threshold for the N3 wave (3 × TN3) in B. The arrows indicate the time of stimulation. With the same intensity as in A (3 × TN1), low-rate burst TENS (3 bursts/sec, 7 pulses/burst, internal frequency 85 Hz) in C and high-frequency TENS (85 Hz) in E seemed not to affect C-fiber evoked responses of the spinothalamic tract cell. With the same intensity as in B (3 × TN3), marked inhibition is shown in D, using the low-rate burst form of TENS, and in F for high-frequency TENS. Note the post-TENS inhibition in both D and F. The brackets in each histogram indicate the period of TENS application.

FIG. 4. Averaged C-fiber evoked responses of spinothalamic tract (STT) cells produced by test stimuli in periods during and after termination of transcutaneous electrical nerve stimulation (TENS) using different stimulation parameters: low intensity (3 × TN1) and high intensity (1.3 to 4.3 × TN3) in both low-rate burst and high-frequency modes. In 13 paired trials with high intensities in 10 STT cells, low-rate burst TENS (filled circles) produced more inhibition than did high-frequency TENS (filled triangles); significant differences (p < 0.05) are indicated by asterisks. Both forms of stimulation caused considerable post-TENS inhibition lasting about 150 seconds after cessation of TENS and showing exponential recovery. Note progressive inhibition at the beginning of low-rate burst TENS, and the abrupt onset of inhibition using high-frequency TENS. In four paired trials in four cells, low-intensity TENS produced no appreciable inhibition with either frequency: open circles, low-rate burst and open triangles, high-frequency TENS. Responses were averaged at 30-second intervals for statistical comparisons. Bars indicate standard deviations of mean values.

there was still 10% inhibition 150 seconds after cessation of TENS. In four cases of low-intensity TENS (3 × TN1 threshold), regardless of frequency, there was no noticeable inhibition either during or after TENS, as shown in Fig. 4.

Other factors influencing TENS inhibition were also examined. The position of the TENS electrodes was varied. Figure 5 shows an example. The TENS parameters were the same in all trials: high intensity (3 × TN1) and low-rate “comfort bursts.” The most marked inhibition of C-fiber responses of STT cells was produced by TENS using two pairs of electrodes (Fig. 5E). When TENS electrodes were placed on the mirror site of the receptive field on the opposite hindlimb, stimulation produced a slight excitation rather than inhibition at the beginning (Fig. 5D).

Usually, TENS was applied by bipolar electrodes with the negative electrode placed as proximally in the receptive field as possible. When the polarity of the electrodes was changed to proximal positive (one trial in each of two cells), inhibition during TENS was less than when the proximal electrode was negative, but both polarities produced the same degree of post-TENS inhibition. The inhibition in periods during and after TENS was significantly reduced both in the cases of TENS application outside the receptive field on the same hindlimb (one trial in each of two cells) and at the mirror site of the receptive field on the opposite hindlimb (one trial in each of four cells). However, if two pairs of TENS electrodes were used, one pair on the receptive field and the other outside the receptive field or on the mirror site on the opposite hindlimb.
TENS inhibition of primate spinothalamic cells

Fig. 6. Average inhibition of C-fiber evoked responses of spinothalamic tract cells produced by transcutaneous electrical nerve stimulation (TENS) applied at different sites: two sites (filled triangles), one pair of electrodes in the receptive field (RF) and the other pair of electrodes outside the RF on the same hindlimb or at a mirror site to the RF on the opposite hindlimb, produced the largest inhibition; the next greatest inhibition resulted from TENS with single pair of electrodes in the RF (filled circles). When applied with a pair of electrodes outside the RF on the same hindlimb (open triangles) and with a pair of electrodes at the mirror site (open circles), TENS had less or no effect. All examples resulted from experiments using the same stimulating parameters: high intensity (3 × TN3) and low-rate bursts, while recording from the same four spinothalamic tract cells, but TENS application outside the RF was tried on only two of the cells. Bars indicate standard deviations of mean values.

Fig. 5. An example of another factor influencing transcutaneous electrical nerve stimulation (TENS) inhibition. Application of TENS was with low-rate bursts at high intensity (3 × TN3) for one cell. A shows the inhibition produced by TENS with placement of proximal-negative distal-positive surface electrodes on the receptive field. B shows slightly less inhibition by TENS using reversed polarity. When the electrodes were outside the receptive field on the same hindlimb, the inhibition was reduced (C), and no inhibition was produced by TENS at the mirror site of the receptive field on the opposite hindlimb (D). There was a slight increase in C-fiber response at the beginning of TENS at the mirror site. The largest inhibition was achieved when TENS was applied simultaneously to two sites, the receptive field and the mirror site, as shown in E.

(one trial in each of four cells), the inhibition was significantly increased both during and after TENS compared with the inhibition produced by only one pair of electrodes placed in the receptive field, as shown in Figs. 5 and 6.

Noxious Heat Stimulation of STT Cells

We have observed the responses of STT cells induced by application of noxious heat to the glabrous skin in the receptive field during and after TENS application (low-rate burst and high intensity, 3 × N3 threshold) in one trial in each of three cells. Figure 7A shows a typical example of the activity of a wide dynamic range STT cell before, during, and after noxious heat (53°C) stimulation for 30 seconds during the time indicated by a solid bracket in the histogram.

For statistical comparisons, we gated and counted the spikes occurring during the first 500 msec of each 5-second period, as shown in Fig. 7B. Control responses to heat were compared to responses after 40 seconds of TENS (starting 10 seconds before heat stimulation), as indicated by a dashed bracket in Fig. 7C. There was strong inhibition of noxious heat-induced responses in periods during TENS (low-rate bursts, high intensity), with progressive recovery, as shown in Fig. 7D (recorded at 5 minutes after the TENS trial). Two of the three STT cells showed inhibition of noxious heat-induced activity during and after TENS. One cell showed no change.
Role of Endogenous Opioids

To investigate a possible involvement of endogenous opioid substances in the inhibition of STT cells produced by TENS, the effect of naloxone hydrochloride on the inhibition was studied. After observing TENS inhibition and its gradual recovery to control level (using both the low-rate burst and high-frequency modes at the high intensity of $3 \times N_3$ threshold), as shown in Fig. 8A and C, naloxone hydrochloride (0.05 mg/kg) was given intravenously. At 5 minutes after naloxone was given, TENS application was repeated with identical stimulus parameters. As illustrated in Fig. 8B and D, there was no difference between the inhibition produced by low-rate bursts or by high-frequency TENS before and after naloxone. The same negative result was obtained in two other cells. This is in contrast to our findings of a prolonged, naloxone-reversible inhibition of the flexion reflex in the cat following peripheral nerve stimulation, but comparable to our observation in a previous study that the inhibition of primate STT cells produced by peripheral nerve stimulation is minimally affected by naloxone.

Inhibition of Responses by TENS Versus Peripheral Nerve Stimulation

In our previous study, peripheral nerve stimulation produced a profound inhibition of primate STT cells. We therefore compared the inhibition produced by TENS with that produced by peripheral nerve stimulation (tibial nerve) using the same stimulation parameters (low-rate bursts and the high intensity of $3 \times N_3$ threshold) on the same cell. Although the receptive field had a tibial nerve distribution, there was more inhibition using TENS than using peripheral nerve stimulation, as shown in Fig. 9A and B. The inhibitory patterns, with gradual onset of inhibition and exponential recovery, were similar.

Effect of TENS on Peripheral Nerve Conduction

We have recorded signal-averaged compound action potentials showing C-fiber volleys evoked by test stimuli applied to the sural nerve to see if peripheral conduction is influenced by TENS. After control recordings of volleys produced by 10 consecutive test stimuli of the sural nerve at 10-second intervals, as shown in Fig. 10A, we repeated an identical series of stimuli so that we could observe the C-fiber volleys immediately after 5 minutes of TENS application (Fig. 10B; low-rate bursts and high intensity, $3 \times N_3$ threshold). We also repeated the volleys 5 minutes after termination of TENS (Fig. 10C). There were no definite changes in latencies or amplitudes of the C-fiber volleys. Two trials in two experiments gave the same findings, suggesting that no substantial alteration in conduction in C-fibers was
TENS inhibition of primate spinothalamic cells

**Fig. 8.** An example of the lack of effect of naloxone on the inhibition of a spinothalamic tract cell produced by transcutaneous electrical nerve stimulation (TENS). A and C are pre-naloxone controls with TENS at a high intensity ($3 \times \text{TN}_3$), in both low burst rate and high-frequency modes, respectively. Five minutes after intravenous injection of naloxone (0.05 mg/kg), identical TENS applied in B (low-rate burst TENS) and in D (high-frequency TENS) produced no appreciable change in the inhibition. Brackets indicate the period of TENS application.

caused by TENS. Oscilloscope observations indicated that the C-fiber volley was not obviously changed during TENS.

**Other Responses Affected by TENS**

In seven paired trials, the responses of four cells to volleys in both A- and C-fibers evoked by test stimuli were compared, using both the low-rate burst and the high-frequency modes of stimulation at the same intensities ($1.6$ to $4.3 \times \text{N}_3$ threshold). The results showed a greater inhibition produced by low-rate burst TENS than by high-frequency TENS ($p < 0.001$). The amount of inhibition tested with A- and C-fiber responses was less than the inhibition tested with just C-fiber responses. This observation suggests that TENS produces some degree of inhibition of A-fiber responses, although not as much as of C-fiber responses.

We could not analyze the background activity during TENS because of the activation of STT cells by TENS.

**Fig. 9.** A comparison of transcutaneous electrical nerve stimulation (TENS) inhibition and peripheral nerve stimulation (PNS) inhibition of a spinothalamic tract cell. Stimulation parameters used were the same: high intensity ($3 \times \text{TN}_3$) and low-rate bursts. The TENS was delivered through surface electrodes on the receptive field, and PNS was applied directly to the tibial nerve at the popliteal fossa in the same hindlimb. The receptive field was innervated by the tibial nerve. Note more inhibition in the period during TENS in A than by PNS in B. Brackets indicate the time of electrical stimulation.
FIG. 10. Effect of transcutaneous electrical nerve stimulation (TENS) on peripheral nerve conduction. Compound action potentials showing the C-fiber volley were evoked and recorded from the sural nerve (conduction distance = 21 mm). The A-fiber volley cannot be seen well at the sweep speed and gain used. A single electrical pulse at an intensity suprathreshold for C-fibers was used for test stimulation at 10-second intervals. Each division on the vertical axis = 200 μV. A: Signal-averaged compound action potentials produced by 10 trials of stimulation of the sural nerve. B: The compound action potentials averaged in the same manner as the control, immediately after 5 minutes of TENS applied to the receptive field. C: Compound action potential recorded 5 minutes after termination of TENS. D: The compound action potentials in A, B, and C have been superimposed. There were no appreciable changes in latencies or amplitudes of the compound action potentials recorded from the sural nerve before and after TENS, although the same TENS produced powerful inhibition of the evoked activity of a spinothalamic tract cell.

The two most commonly employed means of producing analgesia by peripheral stimulation are the ancient Chinese therapeutic procedure known as acupuncture and electrical stimulation of peripheral nerves as used in the West since early times. Acupuncture mechanisms concerned with analgesia, as opposed to effects on many other systems besides the nervous system, are under active investigation in animal models, as well as in human subjects. Transcutaneous electrical nerve stimulation (TENS) has become widely used in medical practice since the study of Wall and Sweet reintroduced electrical stimulation of peripheral nerves as a valid therapeutic modality. Its beneficial results on pain have been compared to the effect of “counter-irritation.” Frequently, the gate control theory, which is focused on segmental spinal inhibitory mechanisms, has been used as an explanation of TENS. However, the mechanisms of acupuncture and TENS analgesia are controversial.

Andersson and others have attempted to relate the characteristics of TENS and acupuncture to the parameters of conditioning stimulation, evoked sensations, analgesic effects, naloxone reversibility, and endorphin release. The essential effects of both TENS and acupuncture appear to be due to increased discharges of afferent nerve fibers that influence the transmission of impulses in pain pathways. The different methodologies employed in these forms of peripheral nerve stimulation may result in activation of various types of afferent fibers in different temporal and spatial patterns.

The present experiments show that TENS at high intensities (1.3 to 4.3 × N₃ threshold), activating Aαβ and Aδ fibers, produced a remarkable inhibition of C-fiber evoked responses in STT cells both during and after TENS application within the receptive field. Inhibition was seen when TENS was applied either with bursts of stimuli repeated at a low rate or with pulses delivered at a high rate. However, TENS at a low intensity (3 × N₁ threshold), activating only Aαβ fibers, produced no inhibition regardless of frequency. Our previous study showed that graded inhibition of primate STT cells is produced by graded intensities of conditioning peripheral nerve stimulation. Consequently, the higher the intensity of TENS, the more profound the inhibition of the responses of STT cells that can be expected. In the present experiments, TENS with a high intensity (higher than the N₃ threshold) produced more inhibition than did low-intensity (lower than N₃ threshold) TENS. If inhibition of STT cells itself. However, the background activity in four paired trials in four cells (low- and high-frequency TENS at the same intensities) could be analyzed after the conclusion of TENS. All of the cells revealed the same pattern. The activity was markedly inhibited immediately after termination of TENS, as in Fig. 2A, followed by an exponential recovery to control level.

Discussion

The two most commonly employed means of producing analgesia by peripheral stimulation are the ancient Chinese therapeutic procedure known as acupuncture and electrical stimulation of peripheral nerves as used in the West since early times. Acupuncture mechanisms concerned with analgesia, as opposed to effects on many other systems besides the nervous system, are under active investigation in animal models, as well as in human subjects. Transcutaneous electrical nerve stimulation (TENS) has become widely used in medical practice since the study of Wall and Sweet reintroduced electrical stimulation of peripheral nerves as a valid therapeutic modality. Its beneficial results on pain have been compared to the effect of “counter-irritation.” Frequently, the gate control theory, which is focused on segmental spinal inhibitory mechanisms, has been used as an explanation of TENS. However, the mechanisms of acupuncture and TENS analgesia are controversial.

Andersson and others have attempted to relate the characteristics of TENS and acupuncture to the parameters of conditioning stimulation, evoked sensations, analgesic effects, naloxone reversibility, and endorphin release. The essential effects of both TENS and acupuncture appear to be due to increased discharges of afferent nerve fibers that influence the transmission of impulses in pain pathways. The different methodologies employed in these forms of peripheral nerve stimulation may result in activation of various types of afferent fibers in different temporal and spatial patterns.

The present experiments show that TENS at high intensities (1.3 to 4.3 × N₃ threshold), activating Aαβ and Aδ fibers, produced a remarkable inhibition of C-fiber evoked responses in STT cells both during and after TENS application within the receptive field. Inhibition was seen when TENS was applied either with bursts of stimuli repeated at a low rate or with pulses delivered at a high rate. However, TENS at a low intensity (3 × N₁ threshold), activating only Aαβ fibers, produced no inhibition regardless of frequency. Our previous study showed that graded inhibition of primate STT cells is produced by graded intensities of conditioning peripheral nerve stimulation. Consequently, the higher the intensity of TENS, the more profound the inhibition of the responses of STT cells that can be expected. In the present experiments, TENS with a high intensity (higher than the N₃ threshold) produced more inhibition than did low-intensity (lower than N₃ threshold) TENS. If inhibition of STT cells...
TENS inhibition of primate spinothalamic cells predicts analgesia, then TENS with a high intensity should be required for the best relief of pain.

Although acupuncture analgesia has been related to the activation of Aoβ or Group II afferent fibers,18,34,58 the present results are in agreement with the experimental findings of Dickhaus, et al., 17 and Woolf, 76 who observed that a suppression of dorsal horn neuronal activity excited by noxious stimuli was produced by high-intensity conditioning stimuli which evoked Aδ and/or C-fiber volley. There are many clinical reports which have shown successful relief of pain in humans with low-intensity conventional TENS.53,75 However, it is common in medical practice to adjust the intensity of TENS to a critical strength,2 such as the level giving forceful muscle contractions or strong beating sensations due to activation of receptors in the deep tissue, or to a level just below that producing pain, in order to produce strong analgesic effects. Although sensory stimulation has a kind of placebo effect,6,66 the pain relief from high-intensity TENS is significantly higher than the placebo contribution,12,49 and it is obvious that the inhibition of STT cells by TENS in anesthetized experimental animals is not a placebo effect.

In the present study, TENS using bursts of pulses repeated at a low rate produced more inhibition than did TENS with high-frequency pulses, using the same high stimulus intensity. This appears to be contrary to the results of others who showed that the conventional high-frequency TENS produced a more effective analgesia in animals and in humans than did low-frequency TENS.48,74 Furthermore, our previous study16 revealed that higher frequency peripheral stimulation inhibited the activity of STT cells more than did lower-frequency stimulation at the same intensity. However, this discrepancy can be explained by differences in the type of low-frequency stimuli used. The low-frequency stimulation used in this study involved bursts of stimuli, rather than low rates of single shocks. These “comfort bursts” simulate the effects of the maneuvers of traditional acupuncture in order to reduce unpleasant sensations associated with high-intensity high-frequency TENS. The strong inhibition of STT cells by this form of TENS is in fact consistent with the findings of others.33,41,49 Consequently, from this and previous peripheral nerve stimulation studies, the mode of conditioning stimulation may be of critical importance for analgesia, as shown by others.5

It has been suggested that TENS due to high-frequency repetitive stimulation interferes with conduction in nociceptive primary afferents of Aδ- and C-fiber caliber, resulting in conduction block or fatigue.10,30,43 Janko and Trontelj52 provide evidence that changes in compound action potentials during TENS result from desynchronization and not from failure of conduction, and they also argue that prolonged post-TENS inhibition could not involve fatigue. Our demonstration that C-fiber volleys show no substantial changes in latency or amplitude in the period during and after TENS is consistent with the observations of Woolf76 that repetitive primary afferent nerve stimulation did not decrease the size of the C-fiber compound action potential or produce a block in conduction in single C polymodal nociceptive afferents in decerebrate rats.

The finding that when TENS is applied outside the receptive field or on the opposite hindlimb it inhibits the activity of STT cells much less than TENS applied in the receptive field is consistent with the clinical observations of Andersson, et al.,3 Jeans,33 and Melzack.49 The polarity of the TENS electrodes seems to be another important factor for TENS inhibition, since more inhibition was found with the proximal electrode negative than with the proximal electrode positive. This observation suggests that the afferent fibers may be activated by TENS within nerve trunks rather than near their peripheral terminals.

Although Nathan and Rudge55 found that noxious heat stimulation was not influenced by TENS of moderate intensity, we found that TENS inhibited the activity of STT cells evoked by noxious heat. This is consistent with the observation of Woolf,76 who reported that TENS applied with high-intensity pulses, giving rise to an unpleasant sensation, caused an elevation of the thermal pain threshold in humans.

The prolonged inhibition, lasting at least 2 minutes after cessation of TENS, can hardly be explained in terms of ordinary synaptic potentials. This suggests the possible involvement of neurohumoral mechanisms such as the release of endorphins or other neuromodulators. There are a few reports concerning direct measurements of these neuropeptides in human cerebrospinal fluid during TENS, but the results reported were contradictory.61,66 Other studies using the opiate antagonist, naloxone, have provided indirect evidence of an involvement of endogenous opioids in TENS.11,78 However, Abram, et al.,1 and Freeman, et al.,21 showed that TENS is not reversible by naloxone in human subjects. Our present and previous studies14,16 have shown very little effect of naloxone on the inhibition of the STT cells by peripheral nerve stimulation, unlike the naloxone-reversible inhibition of the flexion reflex in the cat that we have previously demonstrated.13 Furthermore, various pharmacological blocking agents, including picrotoxin and bicuculline for GABA (gamma aminobutyric acid), strychnine for glycine, mepergolone and phentolamine for serotonin and catecholamines, and substance P inhibitors, had no appreciable effect on the inhibition produced by peripheral nerve stimulation, suggesting a lack of involvement of the corresponding agents in the inhibition.14 Although we did not try to prove this, it is possible that a neuropeptide other than enkephalin or accumulation of K+ in the spinal cord dorsal horn18 could mediate the inhibition found during and after electrical nerve stimulation.

Acknowledgments

We wish to thank H. Wilcockson and G. Gonzales for...
their expert technical assistance, and P. Waldrop for typing the manuscript.

References


34. Kaada B: Mechanisms of acupuncture analgesia. Tidsskr Nor Laegeforen 94:422-431, 1974


41. Le Bars D, Chitour D, Clot AM: Diffuse noxious inhibi-
TENS inhibition of primate spinothalamic cells


Manuscript received April 16, 1984. Accepted in final form August 23, 1984.
This work was supported by Grants NS 09743, NS 11255, NS 18830, and NS 21266 from the National Institutes of Health, and by grants from the Moody Foundation and the American Heart Association, Texas Affiliate.
Present address for Dr. Lee: Department of Neurosurgery, Kosin Medical College, Busan, Korea.
Address reprint requests to: Jin Mo Chung, Ph.D., Marine Biomedical Institute, University of Texas Medical Branch, 200 University Boulevard, Galveston, Texas 77550.