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(Degree)

博士 (保健学)

(Date of Degree)

2006-03-25

(Date of Publication)

2009-04-07

(Resource Type)

doctoral thesis

(Report Number)

甲3658

(URL)

<https://hdl.handle.net/20.500.14094/D1003658>

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博士論文

**Analysis of the analgesic effect of segmental spinal cord evoked potentials elicited by
transcutaneous electrical nerve stimulation**

経皮的末梢神経電気刺激の鎮痛効果に関する分節性
脊髄誘発電位の解析

平成18年 1月10日

神戸大学大学院医学系研究科保健学専攻

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Analysis of the analgesic effect of segmental spinal cord evoked potentials elicited by transcutaneous electrical nerve stimulation

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Transcutaneous electrical nerve stimulation (TENS) can be administered in low-frequency and high-frequency mode. No general consensus has currently been reached regarding the optimal mode. To establish the optimum conditions for TENS and clarify its analgesic effect, segmental spinal cord evoked potentials (SCEP) were elicited in thirty-five male Wistar rats by high-frequency (15) or low-frequency TENS (15) and controls (5). The results indicated that measuring SCEP was meaningful in ascertaining the analgesic effect of TENS. With high-frequency TENS, significant suppression of P1-N1 amplitude ($P < 0.05$) and significant extension of P1 and N1 latencies were confirmed ($P < 0.05$). In contrast, no significant changes in the various components were observed with low-frequency TENS. The results of the present study suggest that high-frequency TENS may suppress pain in the dorsal root and dorsal column of the spinal cord.

Key words : high-frequency TENS low-frequency TENS electrical analgesic effect segmental Spinal Cord Evoked Potentials

Introduction

Ever since Melzack and Wall¹⁾ proposed the gate control theory, transcutaneous electric nerve stimulation (TENS) has been widely performed to alleviate pain electrically.

In 1967, Shealy²⁾ devised an implantable spinal cord electrical stimulator to be placed over the spinal cord, the so-called dorsal column stimulator. In 1973, Long³⁾ devised the implantable percutaneous electrical nerve stimulator. Furthermore, Hosobuchi⁴⁾ have reported the analgesic effects of deep brain electrical stimulation. However, these electrical stimulation methods are considerably invasive and are associated with the complications of skin infection and disconnection of the wire electrodes. Hence, since Ignelzi⁵⁾ reported the electrophysiological and analgesic effects of non-invasive transcutaneous electrical nerve stimulation (TENS), this technique has been widely applied throughout the world⁶⁾.

TENS can be administered in low-frequency (5-20Hz)^{5,15,20,22,30)} and high-frequency (70-100Hz) mode^{16,17,21,31)}. No general consensus has currently been reached regarding the optimal mode; some studies have suggested that high-frequency TENS is more effective while others have favored low-frequency TENS^{17,21,31)}. Moreover, clinical studies⁷⁻¹⁴⁾ have been conducted on the analgesic effect of TENS in patients with chronic pain caused by low back pain⁷⁾, rheumatoid arthritis⁸⁾ or neuritis⁹⁾ and basic studies have been conducted in fields such as neurophysiology¹⁵⁻²¹⁾ and biochemistry²²⁻²⁴⁾, but no conclusive findings have been obtained. Previous studies have suggested that high-frequency TENS causes alternative inhibition of A-delta fiber at a primary neuron level^{15,21)}. Moreover, many reports have documented that low-frequency TENS promotes release of endogenous opioids²²⁻²⁴⁾. In response to the conflicting results of previous studies and the lack of research on the mechanisms through which TENS works, the objective of

the present study was to clarify the electrophysiological effect of TENS on the spinal ascending pathway based on changes in segmental spinal cord evoked potentials (SCEP).

Materials and Methods

All experiments were approved by the Animal Care and Use Committee at the Faculty of Medicine of Kanazawa University.

Thirty-five male Wistar rats weighing from 193 to 285 g (Age:8 weeks, mean body weight: 225.3 ± 30.3 g) were used. These rats were randomly divided into three groups: normal control SCEP was measured in 5 rats; low-frequency TENS was delivered to 15; and high-frequency TENS to 15. Each rat was administered 0.1cc/100g of sodium pentobarbital intraperitoneally to induce general anesthesia. Next, each anesthetized rats was fixed on a brain immobilizer in the prone position and underwent the following surgical procedure (Fig. 1). Using a stereoscopic microscope (OLYMPUS-OME, OLYMPUS KOGYO, JAPAN), a skin incision was placed along the midline of the back, and the fourth, fifth and sixth lumbar vertebrae were exposed while detaching the surrounding muscle tissue. Laminectomy was then performed using a dental reamer. Next, the skin on the lateral side of the left thigh was opened, and the sciatic nerve was exposed while detaching the surrounding muscle tissue to complete surgery.

During the experiments, rectal temperature was monitored using a thermistor-thermometer (TAKARA KOGYO, JAPAN), and body temperature was maintained at 34.0-35.0 °C using a heating pad. Room temperature was maintained at 22 °C by means of air conditioning.

1. SCEP measurement

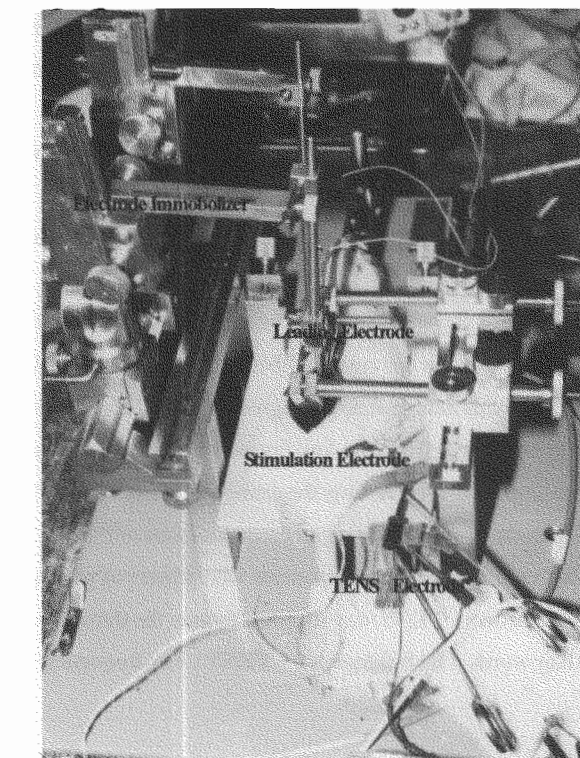


Figure 1. Photograph of the experimental apparatus

SCEP were measured using the Medelec Module Evoked Electromyograph. A bipolar silver electrode was attached to the trunk of the left sciatic nerve and rectangular currents (duration: 200 μ sec, frequency: 1 Hz) were delivered by bipolar stimulation through the stimulus-isolation unit. Intensity of stimulation was set to produce maximum amplitude SCEP (mean: 10.3 ± 0.8 V). A silver-ball electrode (electrode tip diameter: 1 mm) was used as a leading electrode (cathode). This was held using an electrode immobilizer and placed at the spinal segment corresponding to the sciatic nerve; i.e. the dorsal side of the epidural space of the fifth and sixth lumbar vertebrae. A reference electrode (anode) was placed 5 mm proximal to the leading electrode. SCEP was measured before TENS, immediately after TENS and 2, 4, 6, 8 and 10 minutes after TENS.

2. TENS parameters

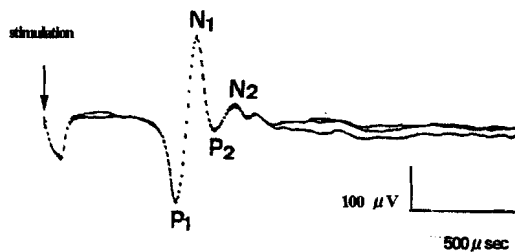


Figure 2. Segmental spinal cord evoked potentials(SCEP) in control rat

TENS was performed using TENS unit (PULSE CURE PRO, KR-7, OG GIKEN, JAPAN). A ring-shaped stimulating electrode was placed on the left lower thigh, and antegrade stimulation was applied continuously for 5 minutes at a duration of 200 μsec. Mean stimulation intensity was 47.5 ± 6.6 V ($4 \times$ maximum SCEP amplitude intensity). The stimulating frequency of TENS was set at either high-frequency TENS (100 Hz) or low-frequency TENS (20 Hz).

3. Data analysis

The amplitude of each SCEP component was measured on a computer screen with a cursor. Amplitude of P1-N1 was measured between the initial positive and subsequent negative deflections. P1, N1 and P2 latencies of each SCEP component were measured at initial peak latency.

Statistical analysis was performed using a one-way analysis of variance (ANOVA); differences were considered statistically significant if p -values < 0.05 . All values were reported as mean \pm SD.

Results

1. Normal control spinal cord evoked potentials

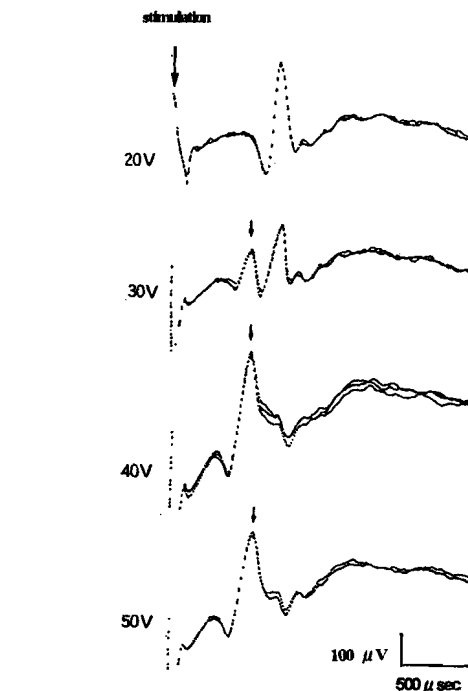


Figure 3. Changes in SCEP with respect to the intensity of stimulation

↓ : a new component appeared in front of the P1 Component

The normal control SCEP of the five Wistar rats was triphasic. The two positive potentials were termed P1 and P2, while the two negative potentials were named N1 and N2. Mean latency was 600 ± 100 μsec for P1, 800 ± 100 μsec for P2, and 700 ± 100 μsec for N1. Mean P1-N1 amplitude was 338.1 ± 49.1 μV (Fig. 2).

2. Changes in waveforms with respect to stimulation intensity

When stimulating intensity was increased from 20 to 50 V, waveforms changed markedly. P1 and N1 were suppressed by increasing the stimulating intensity. At a stimulating intensity of 40 V, both components largely disappeared, and a new component appeared before P1 instead (Fig. 3).

The effect of TENS was accordingly analyzed based on

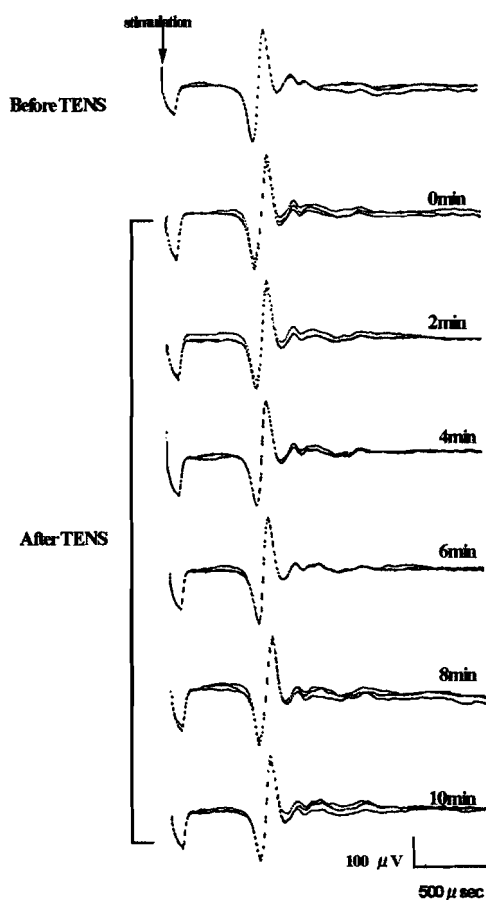


Figure 4. Representative samples of segmental SCEP induced by low-frequency TENS

changes in SCEP waveforms in which P1, N1, and P2 continuously appeared.

3. Changes in SCEP following low-frequency TENS

Figure 4 shows typical chronological changes in SCEP waveforms following low-frequency TENS. No changes in peak latency or amplitude were observed before or after TENS. Mean P1-N1 amplitude (μV) was 343.8 ± 49.5 before TENS, 321.5 ± 32.9 immediately (0min) after TENS, 330.6 ± 40.0 2 minutes after TENS, 333.4 ± 41.9

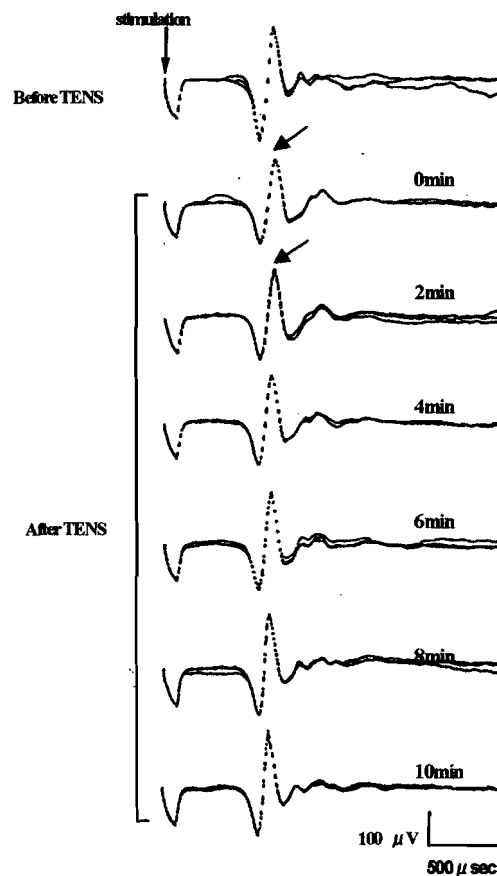


Figure 5. Representative samples of segmental SCEP induced by high-frequency TENS
 \leftrightarrow : decreasing P1-N1 amplitude

4 minutes after TENS, 332.5 ± 38.1 6 minutes after TENS, 333.1 ± 41.9 8 minutes after TENS, and 326.9 ± 47.0 10 minutes after TENS. No statistically significant changes in P1-N1 amplitude were evident before or after low-frequency TENS (Table 1). Mean P1 latency (μsec) was 600 ± 60 before TENS, 600 ± 70 immediately (0min) after TENS, 590 ± 60 2 minutes after TENS, 590 ± 60 4 minutes after TENS, 590 ± 60 6 minutes after TENS, 600 ± 60 8 minutes after TENS, and 600 ± 70 10 minutes after TENS. Mean N1 latency (μsec) was 700 ± 70 before TENS, 690 ± 70 immediately (0min) after TENS, 680 ± 70

Table 1. Changes in P1-N1 amplitude of SCEP before and after TENS

		Before TENS	After TENS					
			0 min	2 min	4 min	6 min	8 min	10 min
Control (N=5)	P1-N1	3381 ± 49.1 <i>μV</i>						
L-FTENS (N=15)	P1-N1	3438 ± 49.5	321.5 ± 32.9	330.6 ± 40.0	333.4 ± 41.9	332.5 ± 38.1	333.1 ± 41.9	326.9 ± 47.0
H-FTENS (N=15)	P1-N1	332.5 ± 48.1	262.8 ± 86.6 *	280.0 ± 72.3 *	305.9 ± 64.2	310.0 ± 58.0	318.6 ± 56.7	302.3 ± 38.0 <i>μV</i>
Mean ±SD			*P < 0.05			L-FTENS: Low-Frequency TENS H-FTENS: High-Frequency TENS		

Table 2. Changes in peak latency of each SCEP component before and after TENS

		Before TENS	After TENS					
			0 min	2 min	4 min	6 min	8 min	10 min
Control (N=5)	P1	600 ± 100						
	N1	700 ± 100						
	P2	800 ± 100 <i>μsec</i>						
L-FTENS (N=15)	P1	600 ± 60	600 ± 70	590 ± 60	590 ± 60	590 ± 60	600 ± 60	600 ± 70
	N1	700 ± 70	690 ± 70	680 ± 70	680 ± 80	680 ± 80	680 ± 80	680 ± 70
	P2	810 ± 80	820 ± 110	820 ± 110	820 ± 110	820 ± 110	800 ± 100	810 ± 90
H-FTENS (N=15)	P1	590 ± 70	610 ± 80*	600 ± 70	600 ± 80	610 ± 70	600 ± 70	600 ± 80
	N1	690 ± 70	720 ± 80*	710 ± 80 *	710 ± 80*	700 ± 80	690 ± 80	690 ± 80
	P2	800 ± 90	850 ± 130	850 ± 110	840 ± 110	840 ± 130	820 ± 110	810 ± 100 <i>μsec</i>
Mean ±SD			*P < 0.05			L-FTENS: Low-Frequency TENS H-FTENS: High-Frequency TENS		

2 minutes after TENS, 680±80 4 minutes after TENS, 680±80 6 minutes after TENS, 680±80 8 minutes after TENS, and 680±70 10 minutes after TENS. Mean P2 latency (*μsec*) was 810±80 before TENS, 820±110

immediately (0min) after TENS, 820±110 2 minutes after TENS, 820±110 4 minutes after TENS, 820±110 6 minutes after TENS, 800±100 8 minutes after TENS, and 810±90 10 minutes after TENS (Table 2). As with amplitude, no

statistically significant changes were observed in peak latency of each component.

4. Changes in SCEP following high-frequency TENS

Figure 5 shows typical chronological changes in SCEP waveforms following high-frequency TENS. P1 and N1 potentials immediately (0min) after TENS were clearly lower than those before TENS. Mean P1-N1 amplitude (μV) was 332.5 ± 48.1 before TENS, 262.8 ± 86.6 immediately (0min) after TENS, 280.0 ± 72.3 2 minutes after TENS, 305.9 ± 64.2 4 minutes after TENS, 310.0 ± 58.0 6 minutes after TENS, 318.6 ± 56.7 8 minutes after TENS, and 302.3 ± 38.0 10 minutes after TENS (Table 1).

Amplitude immediately (0min) and 2 minutes after TENS was significantly lower when compared to that before TENS ($p < 0.05$). However, no statistically significant changes were apparent from 4 minutes after TENS. Mean P1 latency (μsec) was 590 ± 70 before TENS, 610 ± 80 immediately after TENS, 600 ± 70 2 minutes after TENS, 600 ± 80 4 minutes after TENS, 610 ± 70 6 minutes after TENS, 600 ± 70 8 minutes after TENS, and 600 ± 80 10 minutes after TENS. Mean P1 latency was significantly reduced up to immediately (0min) after TENS ($p < 0.05$). Mean N1 latency (μsec) was 690 ± 70 before TENS, 720 ± 80 immediately (0min) after TENS, 710 ± 80 2 minutes after TENS, 710 ± 80 4 minutes after TENS, 700 ± 80 6 minutes after TENS, 690 ± 80 8 minutes after TENS, and 690 ± 80 10 minutes after TENS. Mean N1 latency was significantly reduced up to 4 minutes after TENS ($p < 0.05$). Mean P2 latency (μsec) was 800 ± 90 before TENS, 850 ± 130 immediately (0min) after TENS, 850 ± 110 2 minutes after TENS, 840 ± 110 4 minutes after TENS, 840 ± 130 6 minutes after TENS, 820 ± 110 8 minutes after TENS, and 810 ± 100 10 minutes after TENS (Table 2). No statistically significant change was seen in P2 latency.

Discussion

SCEP elicited in this study were segmental and originated from a spinal segment in response to peripheral nerve stimulation. To the best of our knowledge, the literature contains no studies that investigated the effect of TENS on nerve conductivity by analyzing SCEP. We accordingly took this approach in the present study.

The SCEP basically consists of an initial positive potential (P1), a subsequent sharp negative potential (N1), and then a gradual positive (P2) and negative potential (N2)^{25,30}. These two potentials are always reproduced consistently. It is generally accepted that P1-N1 amplitude reflects the active potential of the spinal dorsal root, while P2-N2 amplitude originates from the dorsal column. Several studies have reported that SCEP waveforms change depending on the location of the leading electrode or the intensity of stimulation. When a leading electrode deviates laterally from the midline of the spine, P1-N1 amplitude increases, while P2-N2 amplitude decreases¹⁷. In terms of stimulation intensity, P1-N1 amplitude has the lowest threshold, while most studies have shown P1-N1 amplitude to be amplified depending on stimulation intensity³⁹. The results of the present study were generally in agreement with those of previous studies.

In terms of the effects of TENS on SCEP, low-frequency TENS did not bring about statistically significant changes in amplitude or latency, but high-frequency TENS significantly suppressed P1-N1 amplitude and significantly extended P1 and N1 latencies. This response lasted two minutes. Kano¹⁷ administered bilateral rectangular currents of 100 Hz to the tibial nerve of 28 adult dogs to elicit SCEP and reported that P1 suppression was mild but N1 and P2 suppression was significant, thus resulting in impulse blockage in the dorsal horn of the spinal cord. Wall³¹ reported that high-frequency TENS (100 Hz) blocked impulse conduction in the peripheral nerve

pathway. Ignelzi⁵⁾ administered low-frequency TENS of 15 Hz to the saphenous nerve of ten mature cats and reported that A-delta fiber impulse was suppressed.

Garrison³²⁻³⁴⁾ reported that impulses in spine dorsal horn cells of cats were inhibited 54% by TENS. In addition, Jiang²¹⁾ considered that high-frequency TENS had a significant effect on a rat model of inflammation. In humans, Levin³⁵⁾ found that that A-delta fiber conduction in the median nerve was inhibited by low-frequency TENS, while Urasaki³⁶⁾ reported that early components of somatosensory evoked potentials (SEP) were inhibited by high-frequency TENS. Furthermore, Akyuz³⁷⁾ reported that SEP and sensory nerve action potentials were inhibited by TENS

In the present study, high frequency TENS significantly lowered P1-N1 amplitude and significantly delayed P1 and N1 latencies for a short period of time, thus suggesting that TENS blocks impulse conduction in the dorsal root and dorsal column of the spinal cord³⁸⁾. Low-frequency TENS did not significantly change SCEP in our study. This finding suggests that further investigations into the mechanism of low-frequency TENS should focus on release of endogenous opioids. In the future, based on the results of the present study, we plan to confirm the therapeutic effects of TENS in clinical settings.

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