Effects on Rats of Low Intensity and Frequency Electromagnetic Field Stimulation on Thoracic Spinal Neurons Receiving Noxious Cardiac and Esophageal Inputs

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■ ABSTRACT

Objective Low intensity and low frequency electromagnetic field stimulation (EMFs) provides substantial pain relief in patients with various chronic pains. The aim of this study was to examine the effects of EMFs on the activity of thoracic spinal neurons responding to noxious visceral stimuli.

Materials and Methods Extracellular potentials of single T_3–T_4 spinal neurons were recorded in pentobarbital anesthetized male rats. A catheter was placed in the pericardial sac to administer a mixture of algogenic chemicals for noxious cardiac stimulation (0.2 mL, 1 min). Noxious esophageal distension was produced by water inflation (0.4 mL, 20 sec) of a latex balloon. EMFs (0.839–0.952 Hz, 0.030–0.034 μG, 30–40 min) was applied with a pair of Helmholtz coils placed on both sides of the chest.

Results After the onset of EMFs, excitatory neuronal responses to intrapericardial chemicals were reduced in 24/32 (75%) spinal neurons, increased in three neurons and were not affected in five neurons. The inhibitory effect on spinal neurons occurred 10–20 min after the onset of EMFs. Even after termination of EMFs, the suppression of spinal neuronal activity lasted for 1–2 hr. In contrast, excitatory responses of 7/18 (39%) neurons to esophageal distension were inhibited, five (28%) were excited and six (33%) were not affected by EMFs.

Conclusions Results showed that EMFs generally reduced nociceptive responses of spinal neurons to noxious cardiac chemical stimuli, whereas it was not effective for nociceptive responses to esophageal mechanical stimulation. ■

KEY WORDS: analgesia, angina pectoris, esophagus, heart, spinal cord, visceral pain

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INTRODUCTION

Numerous clinical studies have shown that electromagnetic field stimulation (EMFs) provides different levels of pain relief in patients with some diseases and neuromuscular disorders (1–7). Also,

this technique has been used in the treatment of various neurological disorders such as multiple sclerosis, epilepsy and Parkinson's disease (1,5,6). In experimental studies, low level EMFs has been shown to affect α- and δ-brain waves (8), to help the regrowth of damaged nerves in mice (9), and to increase the time delay of electrical conduction between the atria and ventricles, as well as to widen the window of vulnerability for atrial fibrillation in dogs (10). Furthermore, low level EMFs has been shown to modulate endogenous opioid activity (e.g., levels of enkephalin and endorphin) and pain behavior in various species including humans (11–17). However, experimental data on physiological effects of extremely low frequency and intensity of EMFs (< 300 Hz, pico-Tesla range) is limited.

The purpose of this study is to examine the effects of EMFs on spinal sensory processing of noxious visceral inputs in rats. Our hypothesis is that low level EMFs modulates spinal neuronal activity, which is evoked by nociceptive cardiac and esophageal afferent inputs. A preliminary report of this work has been published in abstract form (18).

MATERIALS AND METHODS

Experiments were performed on 29 male Sprague-Dawley rats (Charles River Inc., Wilmington, MA) weighing 350–460 g. The protocol was approved by the Institutional Animal Care and Use Committee at the University of Oklahoma Health Sciences Center. Animals were initially anesthetized with a bolus injection of sodium pentobarbital (60 mg/kg, intraperitoneal [ip]) for surgical preparation. Catheters were inserted into the right carotid artery to monitor blood pressure and into the left jugular vein to inject saline and drugs. Pentobarbital (10–15 mg/kg/hr, i.v.) was then infused continuously to maintain the appropriate level of anesthesia throughout experiments. Arterial pressure and pupil diameters were monitored to determine anesthesia level. A tracheotomy was performed for artificial ventilation with a volume-control pump (55–60 strokes/min, 4–5 mL per stroke). Animals were paralyzed with pancuronium bromide (0.4 mg/kg ip) and were given supplemental doses (0.2 mg/kg ip) as needed to maintain muscle relaxation during the experiment. A thermostatically controlled heating pad and overhead infrared lamps were used to maintain rectal temperature between 37 and 38°C.

Laminectomies were performed to expose the T_3–T_4 spinal segments. The animal was mounted in a stereotaxic headholder and stabilized with a clamp at the T_1–T_2 and T_5–T_7 vertebrae. Dura mater on T_3–T_4 segments was removed and the spinal cord was covered with warm agar (3–4% in saline) to improve recording stability. Extracellular potentials of single T_3–T_4 spinal neurons were recorded with carbon-filament glass microelectrodes between 0.5 and 2.0 mm lateral to midline and 0–1.4 mm deep. Cell activity was recorded and stored online with the SPIKE2 data acquisition system (Cambridge Electronic Design, Cambridge, UK). Averaged spontaneous activity was measured for 10 sec and then divided by 10 to determine the mean impulses per second (impulse/sec). Excitatory or inhibitory changes (total impulses) in neuronal activity during a stimulus were calculated as total responses to noxious cardiac or esophageal stimuli.

A silicone tubing (0.020 inside dimension, 0.037 outside dimension, 14–16 cm in length) was passed through the thoracic thymus gland and was inserted into the pericardial sac and over the left ventricle (19,20). A mixture of algogenic chemicals (containing bradykinin, serotonin, prostaglandin E_2, histamine and adenosine) was injected into the pericardial sac for chemical activation of both vagal and sympathetic afferent endings in the heart, because these chemicals may be released during myocardial ischemia (21). All algogenic chemicals were dissolved and mixed in normal saline at concentrations of 10^{-5} mol for each compounds (except adenosine, 10^{-3} mol). The chemical solution (0.2 mL) was injected into the pericardial sac and withdrawn after 60 sec to determine neuronal responses. Intrapericardial chemicals (IC) were rinsed out with 2–3 saline flushes (0.2 mL each). Esophageal distension (ED) was produced by warm water inflation of a small latex balloon (1.0 cm in length) attached to the end of tubing (polyethylene-240). Balloons were inserted perorally into the thoracic esophagus approximately 9–10 cm from the upper front incisors to the end of the tubing (22). The injection of 0.3–0.4 mL of water into the balloon served as the search stimulus. Distension with 0.4 mL water was used to document responses to ED because changes in length and diameter at this

volume are considered a noxious stimulus in rats (22,23). The esophagus was distended two to three times to show that neuronal responses were repeatable and consistent.

Spinal neurons were examined for responses to innocuous and noxious mechanical stimuli applied to the skin. Activity of the high-threshold (HT) neurons increased only with noxious pinching of the somatic field using a blunt forceps. Activity of wide dynamic range (WDR) neurons increased during brushing of the hair or light pressure of somatic fields and it increased even more to noxious pinch. Low-threshold (LT) neurons were activated by hair movement or light pressure but were not excited to a greater extent during noxious pinch. Moving joints (MJ) of the shoulder or forelimb were used as somatic stimuli if a cutaneous receptive field was not found.

To examine the effects of EMFs on the thoracic spinal neurons, a device with a pair of Helmholtz coils (3 × 3 inches in diameter) was placed in parallel on each side of the chest. This location is believed to focus the maximal strength of EMFs onto the heart and esophagus. Two protocols for EMFs parameters were administered. Protocol 1: EMFs at parameters of 0.952 Hz and 0.034 micro-Gauss (μG) was used for 30–40 min. Protocol 2: EMFs consisted of five groups of parameters (0.952 Hz at 0.034 μG; 0.924 Hz at 0.033 μG; 0.896 Hz at 0.032 μG; 0.868 Hz at 0.031 μG; and 0.839 Hz at 0.030 μG). Each parameter was used for 8 min and total EMFs was 40 min. Protocol 2 was carried out to determine if a broader range of amplitudes and frequencies would also affect the esophagus and thereby modulate spinal neuronal activity. These parameters produced the same effects as Protocol 1. Excitatory neuronal responses to two sequential intrapericardial injections (> 15 min) or esophageal distensions (> 5 min) were made to obtain controls. After the control responses were obtained, EMFs was turned on and responses of spinal neurons to IC, ED, or both were examined at intervals of 15–20 min during and after EMFs.

In order to estimate the voltage and current induced by the EMF applied to rat tissue containing thoracic visceral nerves (i.e., a conduction in time-varying EMF), we used the Faraday and Ohm's laws. Using Faraday's law, we estimate the magnitude of the peak induced current $|\bar{J}_{peak}|$ as follows. We assume that a sinusoidally oscillating magnetic field of frequency f and amplitude B_0, $B = B_0(2\pi ft)$, is incident upon a circular loop of the rat tissue of radius r and area πr^2 containing the nerve; thus, the peak voltage induced in the tissue by B is:

$$V_{peak} = \left| \frac{d(\bar{B} \bullet \bar{s})}{dt} \right|_{peak} = 2\pi^2 r^2 f |\bar{B}_0|$$

With $r = 2.5 \times 10^{-3}$ m, $f = 0.952$ H_2, $B_0 = 0.034 \times 10^{-6}$ Gauss, and $V_{peak} = 3.99 \times 10^{-12}$ V. The magnitude of the peak-induced electric field $|\bar{E}_{peak}|$ is equal to the peak voltage divided by the loop circumference:

$$|\bar{E}|_{peak} = \frac{V_{peak}}{2\pi r} = \pi r f |\bar{B}_0|$$

With the same values of r, f, and B_0, $|\bar{E}_{peak}| = 2.5 \times 10^{-10}$ V/m.

From Ohm's law the peak induced current $|\bar{J}_{peak}|$ of a tissue with conductivity σ is

$$|\bar{J}|_{peak} = \sigma |\bar{E}|_{peak} = \pi r f \sigma |\bar{B}_0|$$

Using r for muscle, $\sigma = 0.477$ S/m:

$$|\bar{J}|_{peak} = (0.477 * 2.5 \times 10^{-10}) = 1.19 \times 10^{-10} \text{ A}$$
$$= 1.19 \times 10^{-4} \ \mu\text{A}$$

The V_{peak}, $|\bar{E}_{peak}|$, and $|\bar{J}_{peak}|$ values corresponding to $f = 0.839$ H_3 and $B_0 = 0.030 \times 10^{-6}$ Gauss are $V_{peak} = 3.10 \times 10^{-12}$ V, $|\bar{E}_{peak}| = 1.9 \times 10^{-10}$ V/m, and $|\bar{J}_{peak}| = 9.1 \times 10^{-11}$ A $= 9.1 \times 10^{-5}$ μA.

After the study of the spinal neuron was completed, an electrolytic lesion (50 μA direct current) was made at the recording site. The thoracic spinal cord was removed and placed in 10% buffered formalin solution. Frozen sections (55–60 μm) were examined and the laminae of lesions were identified. Chi-square analysis was used for statistical comparisons of the population of spinal neurons with cardiac and esophageal inputs affected by EMFs. Statistical significance was established as $p < 0.05$.

RESULTS

Responses to Visceral and Somatic Stimulation

Intrapericardial chemicals (IC), esophageal distension (ED, 0.4 mL), or both excited 37 upper thoracic spinal neurons (T_3–T_4). Of these, 19 neurons

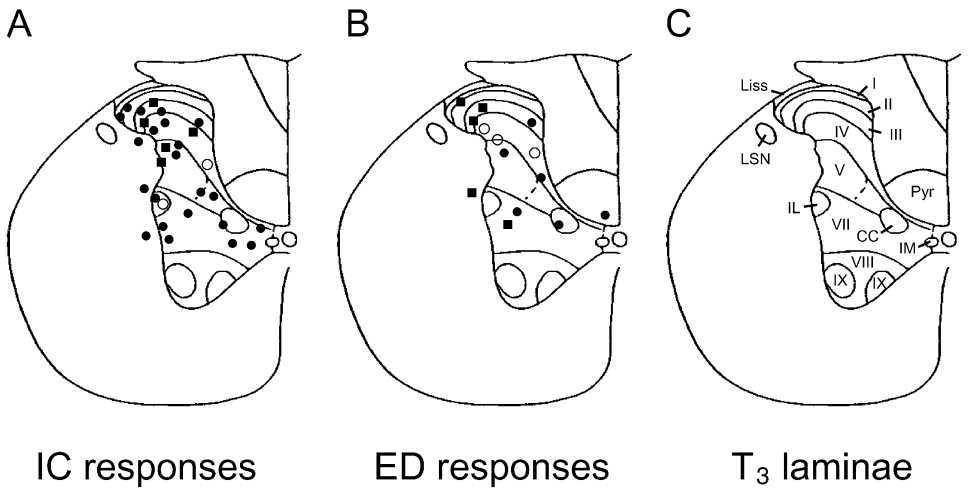

Figure 1. Lesion sites of neurons recorded from thoracic spinal cord. A: Neurons responding to intrapericardial chemicals. ● Neurons inhibited by EMFs; ○ neurons excited by EMFs; and ■ neurons not affected by EMFs. B: Neurons responding to esophageal distension. C: Spinal laminae of gray matter of T_3 segment. IX, Laminae; CC, column of Clarke; IL, intermediolateral nucleus; IM, intermedial nucleus; Liss, Lissauer's tract; LSN, lateral spinal nucleus; and Pyr, pyramidal tract.

were excited only by IC, five neurons were excited only by ED and 13 neurons were excited by both IC and ED. Lesions made at the recording sites in spinal cord were identified histologically, and spinal neurons responding to visceral stimuli were located in superficial (I, II, and III) and deeper laminae (V, VII, and X) of gray matter. Viscero-receptive neurons suppressed and unaffected by EMFs were found in superficial and deeper laminae, whereas all neurons with excitatory responses to EMFs were found only in deeper laminae (Fig. 1). Thirty-four of the 37 (92%) neurons responding to visceral stimuli received convergent inputs from chest, axilla, arms, ears and upper back areas: 16 neurons were classified as WDR, 15 neurons were HT and three neurons responded only to movement of forelimb joints. No significant differences of the effects of EMFs on the proportion of WDR and HT neurons were found.

Effects of EMFs on Responses to IC

No differences in effects between EMFs protocols 1 and 2 were found from the responses of spinal neurons to visceral stimuli (Fig. 2A,B). Therefore, the effects of EMFs on the activity of spinal neurons were combined for analysis. EMFs reduced excitatory responses of 24/32 (75%) spinal neurons to IC (Fig. 2C), increased activity in three neurons and did not affect five neurons during IC (Fig. 2C). Chi-square analysis showed that excitatory responses to IC were more likely to be suppressed than to be intensified by EMFs. Taking all neurons tested for EMFs, the average IC-evoked increases in the activity was reduced from 2453.0 ± 403.7 impulses before EMFs to 1126.2 ± 213.7 impulses ($p < 0.01$) during the onset of EMFs, whereas average spontaneous activity of these neurons did not change (11.8 ± 1.9 impulse/sec vs. 11.9 ± 2.1 impulse/sec). The effects of EMFs usually started 10–20 min after the onset of EMFs and lasted for 1–2 hr. An example of a spinal neuron excited by IC and suppressed by EMFs is shown in Fig. 3G–L. An example of responses to repeated IC without EMFs is shown in Fig. 3A–B. Figure 4 is another example of a spinal neuron with an excitatory response to IC that was suppressed by EMFs. This cell with cardiac input also received convergent inputs from somatic fields and the thoracic esophagus. Figure 5A shows the mean effects and time course of EMFs on excitatory responses of spinal neurons to noxious cardiac stimulus.

Effects of EMFs on Responses to ED

EMFs reduced excitatory responses of 7/18 spinal neurons to noxious ED (0.4 mL), whereas EMFs increased activity in five neurons and did not change activity in six neurons during noxious

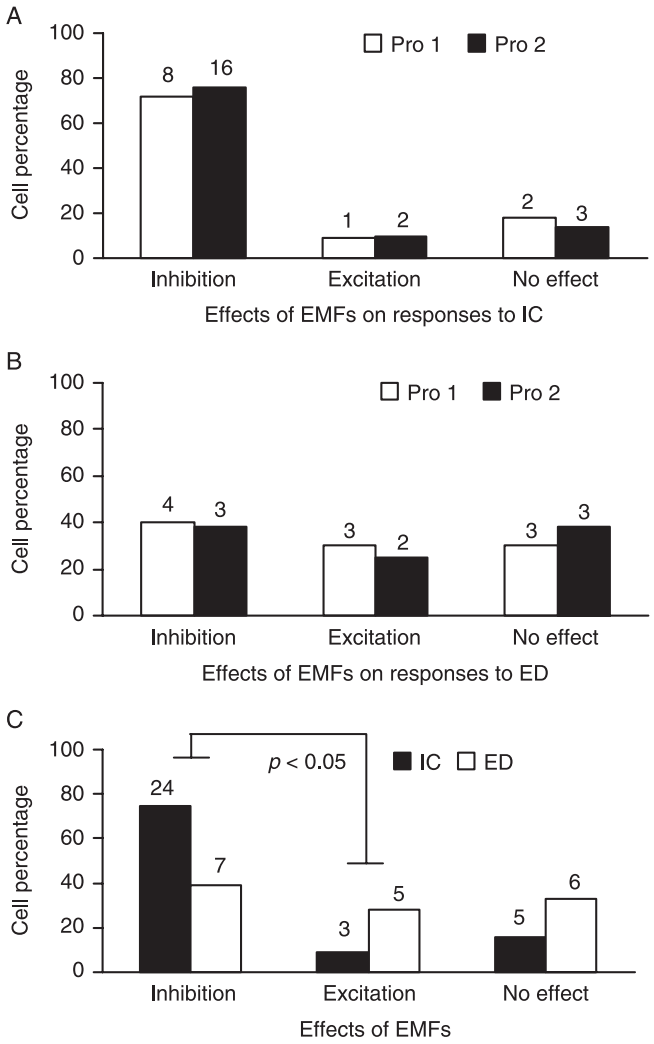

Figure 2. Effects of different parameters of EMFs on thoracic spinal neurons responding to intrapericardial chemicals (IC) and esophageal distension (ED). A: Comparison of effects of protocols 1 and 2 (see Methods) on excitatory neuronal responses to IC. B: Comparison of effects of protocols 1 and 2 on excitatory responses to ED. C: Comparison of total effects of EMFs on responses to IC and ED. The number of cells for each response to protocols 1 and 2 is at top of each bar. The *x* axis shows the percentage of total cells tested with protocols 1 and 2.

ED. No statistical difference was found among the three groups of spinal neurons. Furthermore, no significant differences of mean spontaneous activity (10.3 ± 1.5 impulse/sec vs. 10.9 ± 2.6 impulse/sec) and excitatory ED-responses (325.0 ± 51.3 impulses vs. 343.3 ± 58.3 impulses) for all neurons tested for EMFs before and after onset of EMFs were found. An example of a spinal neuron with an excitatory response to ED that was not affected by EMFs is shown in Fig. 4D–H. Figure 5B shows the mean effects and time course of EMFs on excitatory responses of spinal neurons to noxious esophageal distension.

DISCUSSION

The main finding of this study is that low level EMFs generally reduced nociceptive responses of the upper thoracic spinal neurons to noxious cardiac chemical stimulation, whereas EMFs was not effective for nociceptive responses to esophageal mechanical stimulation in rats. It is possible that the use of EMFs techniques might reduce symptoms of patients with angina pectoris.

Effects of EMFs on Nociceptive Responses

Most neuronal responses of upper thoracic spinal neurons to noxious cardiac and esophageal stimuli in rats are excitatory and a few are inhibitory (19,20,22,23). The present study examined the effect of EMFs on excitatory responses of thoracic spinal neurons to cardiac and esophageal stimuli, as excitation is the predominant response to these stimuli. During and after EMFs, excitatory responses to intrapericardial algogenic chemicals were reduced in 75% of thoracic spinal neurons and the remaining neurons were excited or was not affected. Therefore, EMFs generally suppressed spinal nociceptive responses to chemical activation of cardiac receptors. In contrast, EMFs reduced excitatory responses to ED in only 39% of the neurons, and the remaining cells were either excited or not affected. The difference in the effect of EMFs on responses to noxious cardiac and esophageal inputs might result from activation of different visceral receptors. Intrapericardial injections of algogenic substances mainly activate chemoreceptors on the heart, whereas esophageal distension excites mechanical receptors. Thus, based on this evidence, EMFs modulated afferent activity transmitted in small myelinated and unmyelinated fibers with chemoreceptors in the heart, but this did not significantly affect afferent processing activated by a predominately mechanical stimulus.

Another possible explanation for different effects of EMFs on afferent activity from the heart and esophagus is based on a theory that an

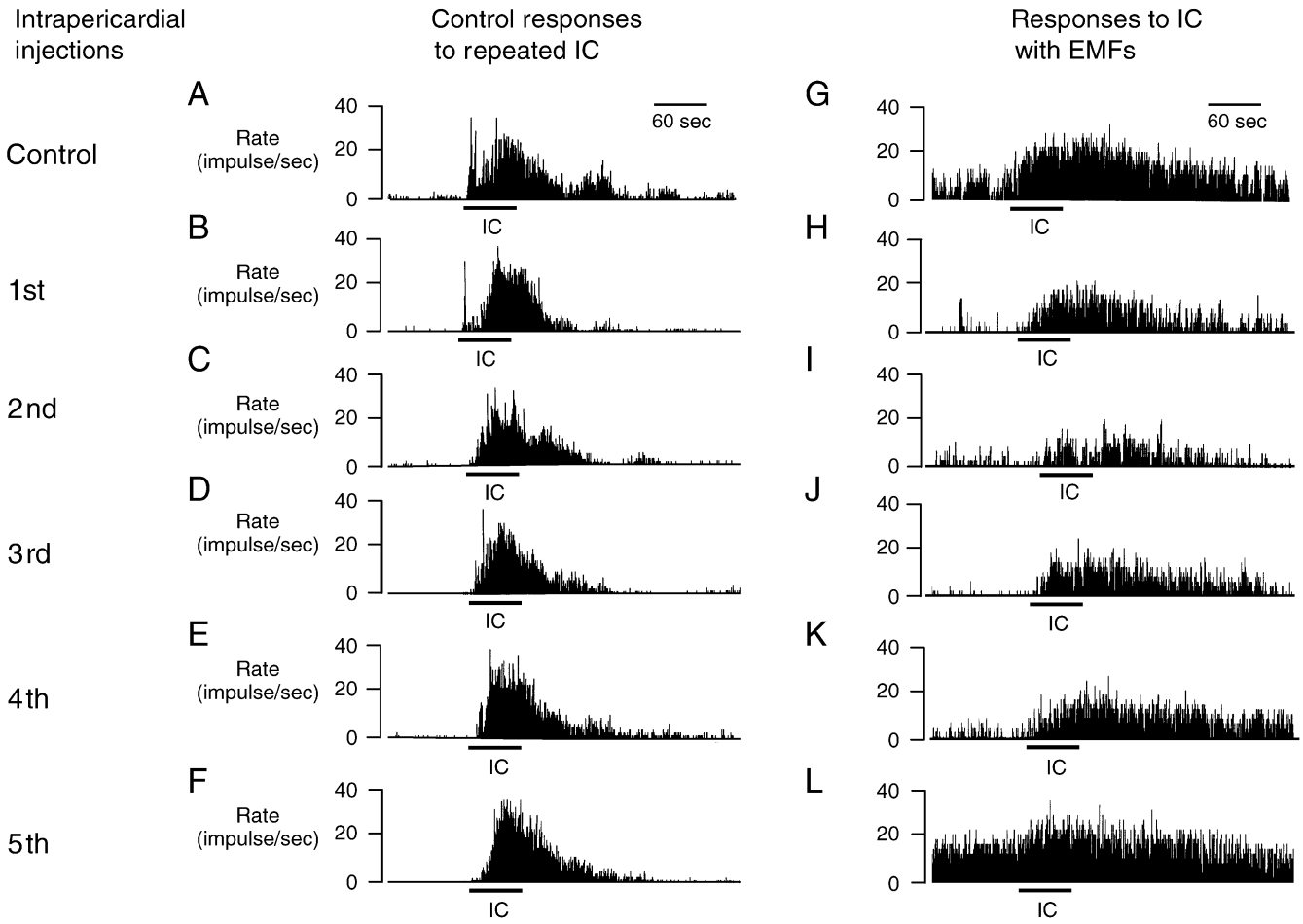

Figure 3. Effects of EMFs on excitatory responses of thoracic spinal neurons to IC. A–F: responses of a spinal neuron to repeated IC. Time from IC control response: 1st IC, 18.4 min; 2nd IC, 36.7 min; 3rd IC, 63.3 min; 4th IC, 81.1 min; and 5th IC, 107.6 min. G–L: inhibitory effect of EMFs on responses of a spinal neuron to IC. Time from IC control response (G): 1st IC, 36.5 min after onset of EMFs; time from removal of 40 min of EMFs: 2nd IC, 16.8 min; 3rd IC, 45.4 min; 4th IC, 73.3 min; and 5th IC, 92.6 min.

optimal "window" exists for the strength or frequency of the magnetic field that affects the specific receptor (16,17). A characteristic of EMFs is that its effects will not be linearly dependent on field parameters such as amplitude or frequency. Rather, the dependence is resonance-like with effects occurring at certain "windows" of the frequency and amplitude of the magnetic field. Thus, EMFs parameters used in this study might be suitable for inhibition of receptors excited by the noxious chemical cardiac stimulus but not be effective for consistent modulation of receptors that are activated with mechanical esophageal distension. An interesting phenomena in this study was that EMFs set at the strength of 0.075 μG and frequency of 2.1 Hz failed to affect the response to cardiac stimulation in a neuron. However, when the EMFs setting was lowered to 0.034 μG and 0.0952 Hz for this same neuron, the response to IC then was inhibited by the electromagnetic field. This observation provided evidence that the EMF strength must lie within this optimal "window" to have an inhibitory effect on spinal neurons. These results suggested that selection of parameters of EMFs might be an important factor to the application of EMFs in research and clinical practice.

Possible Mechanism

The mechanism of EMFs effects at the cellular level is unclear. The strength of EMFs used in this study was similar to that of the earth's magnetic field (24,25). The magnetic component could

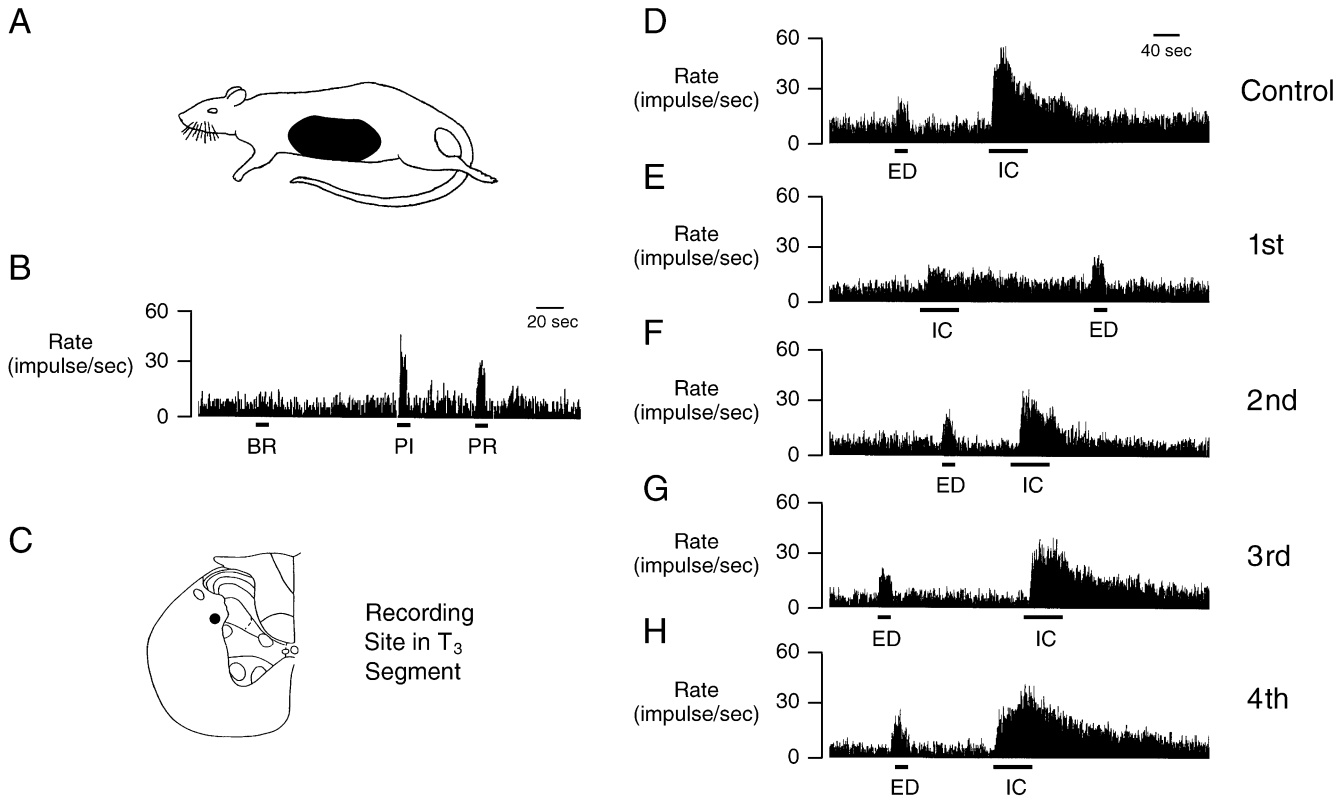

Figure 4. Comparison of effects of EMFs on thoracic spinal neurons responding to IC and ED. A: Location of somatic field of a spinal neuron receiving inputs from the heart and esophagus. B: Responses to brush (BR), pinch (PI) and pressure (PR) of somatic field. C: Lesion of recording site for this neuron in spinal cord. D: Control responses to IC and ED. E–H: EMFs decreased IC-evoked responses of this neuron, but did not affect its responses to ED. Time from onset of EMFs: 1st IC and ED, 17.5 and 21.6 min, respectively, and 2nd ED and IC, 34.2 and 36.5 min, respectively. Time from removal of 40 min of EMFs: 3rd ED and IC, 14.7 and 18.2 min, respectively, and 4th ED and IC, 30.4 and 33.3 min, respectively.

freely pass through the cell membrane whereas the electric component would be hindered as a result of high impedance (9), and the pulsed EMFs would be more active biologically than a constant field (25). A basic mechanism for the action of oscillating EMFs on cells is that an external oscillating EMF could induce forced-vibration of all free ions on the surface of a cell membrane, and this coherent vibration of electric charge is able to irregularly gate electrosensitive channels on the membrane (15–17). Low frequency EMF has the ability to disrupt the cell's electrochemical balance and to alter biochemical events in the cell (e.g. ion flux and chemical reaction rate involving ions) (25–30). For example, Ca^{2+} and K^{+} are key ions and channels that can be resonated with the proper intensity and frequency of EMFs (11,15–17,29). Therefore, it is presumed that the low frequency electromagnetic field used in this study could directly interact with cellular activity of the cardiac nociceptive receptors to modulate neural information traveling in sympathetic afferents from the heart to the spinal cord.

Potential Implication

Low level EMFs has been demonstrated to affect α- and δ-brain waves in humans (8), to enhance regeneration of damaged nerves in mice (9) and to alter atrioventricular conduction and heart rhythm (10). Low level EMFs also modulates endogenous opioid activity (e.g. enkephalin, endorphin) and pain behavioral actions in various species including humans (11,12,14,15,17). Clinically, EMFs has shown some benefits in patients with joint diseases, pelvic pain and neurological disorders such as epilepsy, multiple sclerosis, and Parkinson's disease (1,2,5–7). The results in this study suggested

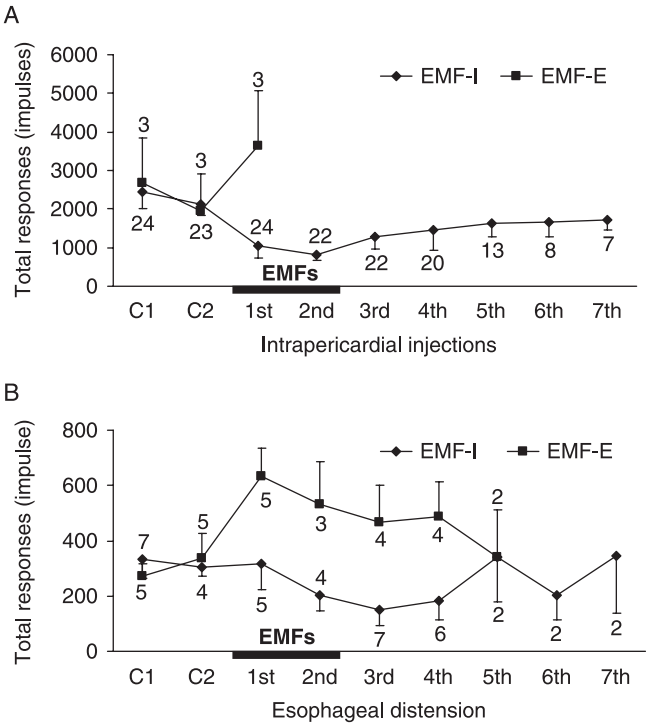

Figure 5. Mean effects of EMFs on excitatory responses of thoracic spinal neurons to noxious cardiac and esophageal stimuli. EMF-I, neurons inhibited by EMFs; EMF-E, neurons excited by EMFs, C1, C2, controls 1 and 2. Number of cells tested at each measurement are shown in the graph. A: Effects of EMFs on spinal neurons responding to IC. Time from onset of EMFs: 1st IC, 16.8 ± 0.5 min, and 2nd IC, 36.8 ± 0.6 min. Time from end of EMFs: 3rd IC, 20.1 ± 0.8 min; 4th IC, 38.9 ± 0.6 min and 5th IC, 61.6 ± 1.3 min; 6th IC, 81.2 ± 1.6 min; and 7th IC, 106.1 ± 1.9 min. B: Effects of EMFs on spinal neurons excited by ED. Time from onset of EMFs: 1st ED, 17.2 ± 0.6 min, and 2nd ED, 37.0 ± 0.9 min. Time from end of EMFs: 3rd ED, 19.7 ± 1.1 min; 4th ED, 42.5 ± 2.0 min; 5th ED, 60.4 ± 2.2 min; 6th ED, 85.2 ± 1.1 min; and 7th ED, 112.6 ± 2.4 min.

that EMFs at appropriate parameters might be effective in reducing cardiac pain. This study provided evidence of a potential application for EMFs at extremely low intensity and frequency for relief of angina pectoris.

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