Inhibition of transient lower esophageal sphincter relaxations by electrical acupoint stimulation

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Zou, Duowu, Wei Hao Chen, Katsuhiko Iwakiri, Rachael Rigda, Marcus Tippett, and Richard H. Holloway. Inhibition of transient lower esophageal sphincter relaxations by electrical acupoint stimulation. Am J Physiol Gastrointest Liver Physiol 289: G197–G201, 2005. First published April 14, 2005; doi:10.1152/ajpgi.00023.2005.—Acupuncture has been shown to modulate visceral sensation and function. Traditionally, stimulation at the Neiguan (pericardial meridian) has been used to treat upper gastrointestinal symptoms. Some of the effects of acupuncture may be mediated through release of endogenous opioids and are reversed by naloxone. Gastric distension is the major trigger for transient lower esophageal sphincter (LES) relaxations (TLESRs). The aim of this study was to investigate the effect of electric stimulation at the Neiguan and naloxone on the TLESRs. In 14 healthy volunteers, electrical acupoint stimulation was applied at the Neiguan and a sham point on the hip in randomized order on the same day. In 12 healthy volunteers, the effects of naloxone (80 μg/kg iv bolus injection) and saline on electrical acupoint stimulation were compared on separate days at least 1 wk apart. Esophageal motility was measured during distension of the proximal stomach with 500 ml of air using a barostat balloon. Electric acupoint stimulation at the Neiguan decreased the rate of TLESRs by ~40% from a median of 6/h to 3.5/h (P < 0.02). Acupoint stimulation had no effect on basal LES pressure, the residual LES pressure during TLESRs, the duration of TLESRs, or gastrointestinal symptoms of fullness, bloating, discomfort, or nausea. The effect of acupoint stimulation was not inhibited by naloxone. Electric acupoint stimulation at the Neiguan significantly inhibits the frequency of TLESRs in response to gastric distention in healthy subjects. This effect does not appear to be mediated through μ-opioid receptors.

Neiguan; naloxone

TRANSMITTED LOWER ESOPHAGEAL sphincter relaxation (TLESR) is the most important mechanism of acid reflux in normal subjects and patients with gastroesophageal reflux disease (GERD) (6). Reflux disease is characterized by a greater incidence of acid reflux during TLESRs than in normal subjects and, in some studies, a higher rate of TLESRs (24). The factors controlling the occurrence and rate of TLESRs and acid reflux have not been well understood, but gastric distension is considered to be the major factor in triggering TLESRs (19), especially after meals. TLESRs are mediated by vagovagal neural pathways integrated in the brain stem by a central pattern generator. Reducing the rate of TLESRs by interrupting such neural pathways either at the afferent nerve or at the brain stem center is a physiologically attractive approach to treat GERD (5). A number of receptors have been identified on the neural pathways that control TLESRs including cholinergic, nitroglic, GABA-B, serotonergic, cannabinoid, opiate, and CCK-A receptors (7). Drugs that act as either agonists or antagonists at these receptors have been shown to inhibit triggering of TLESRs.

Acupuncture has been a traditional treatment in Chinese medicine for thousands of years. Acupuncture and related stimulation, such as prolonged implantation of needles in the scalp or auricles and moxibustion (heat application), can modulate visceral sensation as well as function through stimulation at selected cutaneous acupuncture points (acupoints) along the meridians (channels of acupoints) and have been applied widely in almost every human organ system, including the gastrointestinal system (12). Among acupuncture-like stimulation the more recent development of electrical acupuncture, electric acustimulation, and transcutaneous electric nerve/acupoint stimulation (TENS) appears to be more popular for its noninvasiveness and safety. For instance, transcutaneous electrical acupoint stimulation at the Hukou acupoint (on the dorsal web between the first and second metacarpal bones of the right hand) increased the degree of LES relaxation in volunteers (1) and reduced basal LES pressure in patients with achalasia (4, 11), an effect that is not observed when stimulation was applied to nonspecific skin of the dorsum of the hand, irrelevant to any traditional meridians (18). In addition, electric acupoint stimulation at Neiguan (on the pericardial meridian) reduces the perception to gastric distension (3), relieves vector-induced dysrhythmia (9), and normalizes gastric dysrhythmia (15) in human subjects.

Precise mechanisms for the effects of acupuncture have not been extensively investigated and are not fully understood. Some reports have documented that the effects of acupuncture can be abolished by local anesthesia at the acupoints or nerve block, and partially by vagotomy (26). Acupuncture has also been found to release certain neurotransmitters, particularly the β-endorphins and met-enkephalin, from nerve endings to exert biological effects (16). Naloxone has been shown to reverse some of the effects of acupuncture suggesting that the μ-opioid receptor may be involved (10, 14, 27).

Because data on the effect of electric acupoint stimulation on esophageal motor function are limited, the aim of this study was to investigate the effect of electric stimulation at the traditional acupoint Neiguan on triggering of TLESRs and the effect of μ-opioid receptor antagonist naloxone in healthy volunteers.
MATERIALS AND METHODS

Subjects

Fourteen subjects (12 men and 2 women) ages 19 to 63 yr (median 34 yr) with a mean body mass index of 25.0 ± 0.8 kg/m² were studied for protocol 1. All subjects had no gastrointestinal symptoms, no history of upper gastrointestinal surgery, and no family history of epilepsy and were not taking regular antacids or medications known to influence esophageal motor function. Twelve healthy volunteers, 8 men and 4 women, ages 21 to 58 yr (median 35 yr) with a mean body mass index of 27.6 ± 1.4 kg/m², four of whom had participated in protocol 1, were recruited for protocol 2. None was using opioid agents or was known to be hypersensitive to naloxone. Each subject gave written informed consent, and the protocol was approved by the Research Ethics Committee of the Royal Adelaide Hospital.

Recording Methods

Esophageal motility was performed with a 4.2-mm diameter silicone multilumen manometry assembly (Dentsleeve, Wayville, South Australia) (13). LES pressure was measured with a reverse perfused sleeve sensor (25). Two side holes, one in the distal margin of the sleeve, the other 10 mm more distal, were used to record gastric pressure. Side holes, spaced at 3-cm intervals starting at the proximal margin of the sleeve sensor, monitored pressure at seven sites along the esophageal body. A side hole in the pharynx recorded swallowing. The catheter was fixed and maintained in a position so that the midposition of the sleeve sensor was located within the lower esophageal sphincter. Side holes were perfused with degassed distilled water at 0.15 ml/min and the sleeve sensor at 0.3 ml/min by a low-compliance pneumohydraulic capillary perfusion system.

TLESRs were triggered by distention of the proximal stomach with an electronic barostat (Distender Series III; G & J Electronics, Willowdale, ON, Canada). The lumen used by the barostat for delivery of air into the barostat bag and sensing of pressure within the bag were incorporated within the manometric assembly. The polyethylene bag had a capacity of ~1,100 ml. The proximal portion of the polyethylene bag was tied to the manometric assembly 60 mm distal to the sleeve sensor. The barostat cylinder introduced or withdrew air from the bag at 30 ml/s via an oval channel measuring 1.9 × 2.4-mm internal diameter and 1,570 mm in length. Pressure in the bag was sensed via a lumen of 0.6-mm internal diameter that opened directly into the bag.

Data from the pressure transducers and barostat were recorded on a personal computer (PowerPC 7100; Apple Computer, Cupertino, CA). Manometric data were digitized at 10 Hz using a NBMI016 A-D board (National Instruments, Austin, TX). Barostat data were acquired at 1 Hz via a serial interface. A custom written program (by G. Hebbard, Royal Melbourne Hospital, Melbourne, Australia) using Labview (National Instruments) controlled the barostat and acquired both manometric and barostat data. Data were subsequently imported into Acqknowledge (Biopac Systems, Santa Barbara, CA) for analysis.

Transcutaneous Electric Nerve Stimulation

Transcutaneous electric nerve stimulation at the acupoint was delivered through disc electrodes taped to the skin using a portable nerve stimulator (DYNEX III Neurostimulator; Philips Medical Applications), commonly used in management of chronic pain. Pulse frequency was adjusted to 100 Hz, pulse duration 0.1 ms, and intensity 10–20 mA, which was usually just perceptible but not painful to the subjects. Active stimulation was applied at Neiguan on the nondominant side, which is located between the tendons of palmaris longus and flexor carpi radialis 3 cm proximal to the palmar crease. This acupoint, which is away from the dermatomes associated with esophagus, is on the traditional acupuncture meridian judged to be specific to esophagogastric disorders, such as belch, hiccup, nausea, and vomiting and was selected because gastric distension is the major trigger for TLESRs. Control stimulation was applied at the hip on the same side as the acupoint, a point away from the traditional meridians and dermatomes. The reference electrode was fixed to the interscapular region of the back.

Assessment of Symptoms and Sensations

Upper gastrointestinal symptoms were assessed by questionnaires. Sensations of abdominal bloating, abdominal discomfort, fullness, nausea, hunger, and desire to eat, were measured using a 100-mm visual analog scale before balloon inflation and every 15 min afterward until the end of each study period.

Study Protocol 1: Effects of Electrical Acupoint Stimulation on Lower Esophageal Sphincter Motor Function

Active and control stimulations were tested on the same day in a single-blind randomized crossover design (Fig. 1). Subjects were studied after an overnight fast. The manometric assembly, with the barostat bag folded around it, was passed via an anesthetized nostril into the proximal stomach. The barostat bag was initially unfolded by inflation with 500 ml of air under controlled pressure (<20 mmHg). The bag was then deflated, and the manometric assembly was positioned so that the sleeve sensor straddled the LES, thereby positioning
the barostat bag in the proximal stomach. Subjects were allowed to accommodate to the assembly for 15 min. All studies were performed with the subjects sitting upright in an ergonomic chair designed to minimize abdominal compression.

After the assessment of symptoms, the barostat balloon was inflated with 500 ml of air for 30 min of baseline recording. TENS was then applied to either the Neiguan or sham point in random order for 60 min. TENS was then ceased, and the balloon was deflated for a 60-min washout period. The balloon was then reinflated for another 30-min baseline recording after which TENS was reapplied to either the Neiguan or sham point for 60 min.

Study Protocol 2: Effect of Naloxone on Inhibition of TLESRs by Electric Acupoint Stimulation

The study was of randomized double-blind design comparing naloxone (80 μg/kg) with saline placebo. This dose of naloxone has been shown to completely block the inhibitory effects of morphine (100 μg/kg) on swallow-induced LES relaxation and triggering of TLESRs (22). Naloxone and saline were tested on separate days at least 1 wk apart (Fig. 1). On each study day, after intubation and 15-min accommodation, a bolus intravenous dose of normal saline was given; TENS was applied at the sham point, and the barostat was inflated with 500 ml of air for 60 min. After a 30-min washout period without either balloon distension or TENS, naloxone or saline was given on separate days in a randomized order. TENS was then applied at Neiguan and the bag reinflated for 60 min.

Data Analysis

All manometric traces were coded and read by two reviewers who were blinded to the nature of the stimulus and the drug given. Basal LES pressure was measured at end expiration relative to gastric pressure. Basal LES pressure and intragastric pressure were measured as 1-min visual means for every 15 min at each period of the study for each subject, and an overall mean for each period of the study was calculated. TLESRs were defined and counted separately over the 60 min of each period for each subject with gastric distention according to established methods (8).

Statistical Analysis

The number of TLESRs were compared using Wilcoxon signed-rank test and expressed as median (interquartile range). Basal LES pressure, residual LES pressure during TLESR, duration of TLESR, intragastric pressure, and visual analog scales were presented as means ± SE and were compared using repeated-measures ANOVA was performed (SuperAnova; Abacus Concepts, Berkeley, CA). The data from the two 30-min baseline periods were combined to make an effective 60-min baseline period. A P value of <0.05 was accepted as indicating statistical significance.

RESULTS

Protocol 1: Effects of Electrical Acupoint Stimulation on Lower Esophageal Sphincter Motor Function

Basal LES pressure. Basal LES pressure remained stable during each period of gastric distention. Acupoint stimulation had no effect on basal LES pressure. Overall mean basal LES pressure during electrical acupoint stimulation at Neiguan (10.5 ± 2.3 mmHg) was similar to that during sham stimulation at the hip (11.6 ± 2.1 mmHg) and during the baseline period without any acupoint stimulation (11.1 ± 2.3 mmHg).

Transient LES relaxations. The rate of TLESRs during acupoint stimulation at Neiguan [3.5 per hour (range, 2–6)] was significantly lower than that during both the baseline period without any stimulation [6 per hour (range, 5–8)] and the period of sham stimulation at the hip [6 per hour (range, 4–8); P < 0.02] (Fig. 2).

Sensation. The symptom scores for abdominal bloating, abdominal discomfort, fullness, and nausea were low and ranged between 10 and 35 on the 100-mm visual analog scale. Acupoint stimulation at Neiguan had no effect on gastrointestinal symptoms, and scores were similar during sham and active stimulation periods.

Protocol 2: Effect of Naloxone on Inhibition of TLESRs by Electric Acupoint Stimulation

Basal LES pressure. During saline infusion, basal LES pressure during active stimulation (13.3 ± 1.7 mmHg) was similar to that during sham stimulation (12.8 ± 15 mmHg). Naloxone had no effect on basal LES pressure, and pressures during active stimulation (13.4 ± 1.9 mmHg) were similar to those during sham stimulation (16.8 ± 1.9 mmHg) as well as to those during saline.

Transient LES relaxations. During saline infusion, electrical acupoint stimulation again inhibited triggering of TLESRs with the rate during active stimulation at Neiguan [3 per hour (range 3–4)] being significantly lower than during sham stimulation [6.5 per hour (range, 5–7); P < 0.01] (Fig. 3). However, during infusion of naloxone, the rates of TLESRs were not significantly different during active and sham stimulation [6 per hour (range, 4–7) vs. 5.5 per hour (range, 3–8)] and not significantly different from those during sham stimulation during saline infusion. Acupoint stimulation at Neiguan had no effect on either the residual LES pressure during TLESRs (sham, 0 ± 0.4 mmHg; Neiguan, 0 ± 0.4 mmHg) or the duration of TLESRs (sham, 18.2 ± 1.2 s; Neiguan, 19.1 ± 1.3 s). Likewise, these variables were also not affected by naloxone.

Intragastric pressure. Proximal gastric barostat balloon distention was followed by an increase in intragastric pressure. However, neither acupoint stimulation at Neiguan nor naloxone had any effect on gastric pressure (Fig. 4).

Sensation scores. As in protocol 1, electrical acupoint stimulation at Neiguan had no effect on gastrointestinal sensation. Naloxone also had no effect.

![Fig. 2](http://ajpgi.physiology.org/). Effects of electric acupoint stimulation on the rate of TLESRs triggered by 500-ml-volume controlled gastric distention.
are conveyed to the spinal cord via peripheral nerves and that studies have shown that the sensory impulses of acupuncture nervous system and peripherally on vagal afferents. A number of studies investigate the effect of electric acupoint stimulation on TLESRs. We found that electric stimulation at the acupoint Neiguan resulted in a significant 40% reduction of the frequency of TLESRs induced by gastric distension, a finding that was reproducible in both phases of the study. This degree of inhibition is comparable to that seen with pharmacological agents (5, 7). Because electric stimulation is readily available and is currently widely used in long-term management of chronic pain, these findings suggest that electrical acupuncture may potentially offer an alternative or adjunct treatment for some patients with GERD.

Neiguan was chosen as the acupuncture point for this study. While acupuncture has been used to treat gastrointestinal symptoms in oriental countries for several millennia, scientific evaluation of the effects of acupuncture has been limited. The most commonly used acupoints in treating gastrointestinal symptoms are Neiguan and Zusanli. Traditionally, acupuncture at Neiguan has been used to treat hiccups, belching, nausea, and vomiting. Electric acupoint stimulation at Neiguan has been found to be effective in the management of postoperative nausea and vomiting, relieves vention-induced gastric dysrhythmia, reduces the perception to gastric distention, and normalizes gastric arrhythmia (3, 15). Electrical stimulation at Hukou has been shown to increase the degree of LES relaxation in healthy volunteers (1) and decrease basal LES pressure in patients with achalasia (4, 11). However, because gastric distension is the major trigger for TLESRs, Neiguan appeared to be a more relevant site for affecting triggering of TLESRs than did Hukou.

TLESRs are mediated by vagovagal neural pathways integrated in the brain stem by a central pattern generator (17, 19). The site at which electric acupoint stimulation acts to inhibit the triggering of TLESRs has yet to be determined and was not investigated specifically in this study. However, indirect evidence exists to support actions both centrally within the central nervous system and peripherally on vagal afferents. A number of studies have shown that the sensory impulses of acupuncture are conveyed to the spinal cord via peripheral nerves and that the effects of acupuncture on gastrointestinal motility can be abolished by local anesthesia at the acupoint, by regional nerve block, partially by vagotomy, and by lesions in the brain stem (12). According to traditional Chinese medicine, the hypothesis of acupuncture is that there are 12 main channels running over the body and connecting internal organs. Needling acupoints along these channels regulates vital energy to influence organ function. Anatomic investigations have found that afferent fibers innervating Zusanli are mostly myelinated, large-sized, and A-B fibers (16). Acupuncture stimulation therefore could activate somatic A-B fibers that convey the stimulation to the spinal cord at which level it modulates visceral and other sensory input by a somatovisceral reflex. Such effects have been shown on gastric motility in rats (23). It is possible, therefore, that electric stimulation at Neiguan inhibits the frequency of TLESRs through reducing the sensory input from gastric distention. It is unlikely that electric acupoint stimulation at Neiguan exerts its action primarily on the effector motor pathway, because it had no effect on either the residual LES pressure during TLESRs or on the duration of TLESRs. Whether gastric distension triggers TLESRs through tension or stretch receptors remains controversial (2, 21). Nevertheless, because the distension volume was kept constant and because acupoint stimulation did not affect gastric pressure, it seems unlikely that it was acting through alterations in gastric motility. The mechanism of inhibitory effect of electric acupoint stimulation on triggering of TLESRs thus remains to be elucidated.

Opioid receptors are present in the vagal reflex pathway that mediates TLESRs. Morphine inhibits triggering of TLESRs, an effect blocked by the µ-opioid antagonist naloxone (20). Evidence exists to support the notion that some of the effects of acupoint stimulation are mediated via opioid receptors (12). Acupuncture has been shown to release β-endorphin and met-enkephalin, and application of the electro-acupuncture at different frequency ranges can differentially release the β-endorphin and met-enkephalin. The gastrointestinal actions of exogenous opioid peptides and of acupuncture are similar. Naloxone has been shown to reverse some of the effects of acupuncture. Despite confirmation of the reduction in the rate of TLESRs by electric acupoint stimulation at the Neiguan in the second phase of the study, naloxone, in a dose that had been shown previously to reverse the effects of morphine on the LES (22) had no significant effect on inhibition of TLESRs by
acupoint stimulation. These findings would suggest that \( \mu \)-opioid receptors are not involved in acupункture-induced inhibition of TLESRs. However, the possibility that the dose of naloxone was incorrect or that there was a type 2 statistical error cannot be completely excluded.

The few studies to date on the effects of electric acupoint stimulation on esophageal motility have been limited to effects of stimulation at Hukou on basal LES pressure and swallow-induced LES relaxation. In healthy volunteers, transcutaneous electrical stimulation at Hukou has been reported to increase the degree of LES relaxation to dry swallows. In patients with achalasia, electrical stimulation at Hukou has been shown to decrease basal LES pressure and increase swallow-induced LES relaxation. The findings of the effect of electric acupuncture may help to further study. In addition, knowledge of the underlying mechanisms of TLESRs and reflux in patients with GERD, however, awaits additional study. In summary, electric acupoint at the Neiguan significantly inhibited the rate of TLESRs triggered by gastric distention in normal subjects. These findings suggest a potential therapeutic role for electric acupoint stimulation in the treatment of GERD. The efficacy of electric acupuncture in reducing the frequency of TLESRs and reflux in patients with GERD, however, awaits further study. In addition, knowledge of the underlying mechanisms of the effect of electric acupuncture may help to identify target sites for therapeutic intervention on TLESRs.

REFERENCES