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### **The Basic Science Mechanisms of TENS and Clinical Implications**

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For years, clinicians have been using transcutaneous electrical nerve stimulation (TENS) in an attempt to manage pain. TENS is defined by the American Physical Therapy Association as the application of electrical stimulation to the skin for pain relief. Frequency, intensity, and pulse duration of the stimulation can be varied. Conventional TENS is the most common mode used clinically and uses high frequency (>50 Hz) and low intensity (below motor contraction, sensory only) stimulation parameters. Another common mode of stimulation uses low frequency (<10 Hz) and high intensity (motor contraction) stimulation parameters (Robinson & Snyder-Mackler, 1995). Further, increasing stimulation intensity to produce a painful noxious response is usually given at low frequencies, is called acupuncture-like TENS and is the least common (Robinson & Snyder-Mackler).

#### **History**

The use of TENS in the management of pain began as a presurgical screening for chronic pain patients to determine candidates for implantation of spinal dorsal column stimulators (Burton, 1975; Buton & Maurer, 1974; Wall & Sweet, 1967; Woolf & Thompson, 1994). However, patients reported substantial pain relief following TENS treatment and thus did not even require implantation of the dorsal column stimulator. Since that time, numerous studies have attempted to determine the effectiveness of TENS treatment for individuals with a variety of pain conditions (Feine & Lund, 1997; Nolan, 1988; Robinson, 1996). However, much of the published research shows conflicting data about the actual efficacy and duration of the effect of TENS application. Several factors may contribute to these conflicting reports, including (a) unspecified stimulation parameters, (b) stimulus variables not controlled during the research process, (c) different outcome measures, (d) different electrode placements, (e) lack of placebo control, (f) patients presenting at different stages in the disease process, and (g) failure to monitor or document patient compliance (Kumar & Redford, 1982; Levy, Dalith, Abramovici, Pinkhas, & Weinberger, 1987; Mannheimer & Carlsson, 1979; Mannheimer, Lund, & Carlsson, 1978; Robinson, 1996; Reitman & Esses, 1995). Using animal models allows one to systematically control these variables and begin to decipher the mechanisms of action of TENS. Understanding the mechanisms of action of TENS should help the clinician to better treat patients and clinical researchers to design better outcome studies. Recent studies have begun to uncover the neurological processes involved in TENS analgesia. This review will focus on the mechanisms of action of TENS.

#### **Mechanisms of action**

Studies typically refer to the gate control theory of pain to explain the effects of high-frequency TENS. Specifically, it is suggested that stimulating large diameter afferent fibers inhibits input from small diameter afferent fibers in the substantia gelatinosa of the spinal cord

(Melzack & Wall, 1965; Wall & Sweet, 1967). This is thought to be a segmental inhibition that does not involve descending inhibitory pathways. A commonly held theory for the mechanism of action of low-frequency TENS is activation of endogenous opioid pathways. Analgesia produced by low-frequency, high-intensity TENS but not high-frequency, low-intensity TENS is reversed by administration of naloxone, an opioid receptor antagonist (Sjolund & Eriksson, 1979). Similarly, high-frequency TENS is unaffected by systemic naloxone in patient populations (Abram, Reynolds, & Cusik, 1981; Freeman, Campbell, & Long, 1983). High-frequency TENS is therefore believed to work through mechanisms proposed by the gate theory, producing only short-term analgesia (Garrison & Foreman, 1994; Hollman, 1997). However, the dose of naloxone used in human subjects would be expected to block  $\mu$  opioid receptors. In contrast, analgesia induced in rats by high-frequency TENS is reversed by higher doses of naloxone that non-specifically block  $\mu$ ,  $\delta$ , and  $\kappa$  opioid receptors (Han, Xie, Ding, & Fan, 1984; Woolf, Barrett, Mitchell, & Myers, 1977).

Concentrations of  $\beta$  endorphins increase in the bloodstream and cerebrospinal fluid of healthy patients following administration of either high- or low-frequency TENS (Hughes, Lichstein, Whitlock, & Harker, 1984; Salar, Job, Mingrino, Bosio, & Trabucchi, 1981). Increased concentrations of methionine enkephalin, a  $\delta$  opioid agonist, and dynorphin A, a  $\kappa$  opioid agonist, are observed in the lumbar cerebrospinal fluid following treatment of patients with either low- or high-frequency TENS, respectively (Han et al., 1991). This suggests that at the spinal level there are different opioids released with different stimulation frequencies and thus possibly different opioid receptors activated to produce analgesia with high- or low-frequency TENS. Taken together, these data indicate that several opioids and their receptors may be involved in relief of pain by TENS.

Because low-frequency TENS is usually given at intensities that produce motor contraction (high intensity) and high-frequency TENS is given at lower intensities that produce a sensation without motor contraction (low intensity), it is unknown if the effects of TENS are a result of differences in frequency or intensity. Hyperalgesia, an increased response to a noxious stimuli, occurs in response to tissue injury. Hyperalgesia can occur at the site of injury, termed primary hyperalgesia, and is thought to reflect changes in primary afferent fibers although central neuronal changes will influence primary hyperalgesia. Secondary hyperalgesia also develops outside the site of injury and is thought to reflect an increase in central neuron excitability. Primary and secondary hyperalgesia occur in response to heat and mechanical stimuli following tissue injury (Garry & Hargreaves, 1992; King & Sluka, in press; Lamotte, Shain, Simone, & Tsai, 1991; Ren, Williams, Hylden, Ruda, & Dubner, 1992; Sluka & Westlund, 1993). Because TENS is typically given following tissue injury it is important to measure effects on hyperalgesia. Effects on primary hyperalgesia were examined using the carrageenan paw inflammation model in rats and measuring responses to heat and mechanical stimuli. Effects of varying frequency (4 Hz and 100 Hz), intensity (sensory/low and motor/high) and pulse duration (100 ms and 250 ms) were examined (Gopalkrishnan & Sluka, 2000). Varying frequency, but not intensity or pulse duration, significantly reduces primary heat and mechanical hyperalgesia such that high-frequency TENS reduces the hyperalgesia and low-frequency TENS had no effect. The effect on primary heat and mechanical hyperalgesia is partial, producing only a small reduction but lasting through 24 hours after treatment (Gopalkrishnan & Sluka). In contrast, both low- and high-frequency TENS fully reverse secondary heat hyperalgesia (Sluka, Bailey, Bogush, Olson, & Ricketts, 1998) and nearly reverse secondary mechanical hyperalgesia (King & Sluka, in press) after induction of knee joint inflammation with kaolin and carrageenan. The effects of low- and high-frequency TENS on secondary hyperalgesia are similar and long lasting, 12 to 24 hours after treatment (Sluka et al., 1998; King & Sluka). In a model of neuropathic pain induced by tight ligatures placed around the sciatic nerve, high-frequency, low-intensity TENS, applied segmentally to the skin unilaterally in the lumbar regions L1 through L6, reduces heat but not mechanical hyperalgesia (Somers & Clemente, 1998). This inhibition of heat hyperalgesia only occurs if TENS was started in the first day after injury but not if started 3 days after treatment (Somers & Clemente). Thus, TENS has different effects depending on outcome measures (primary versus secondary hyperalgesia), animal models (inflammatory versus neuropathic), and stimulation parameters (frequency, intensity, pulse duration) used.

Either high- or low-frequency TENS produces an inhibition of spinothalamic tract cells in normal animals without tissue injury (Garrison & Foreman, 1994; Lee, Chung, & Willis, 1985). Garrison and Foreman (1997) recorded from dorsal horn neurons in cats and examined the effect of varying frequency, intensity, and pulse duration on the inhibition of dorsal horn cell activity by TENS. Specifically, increasing intensity, frequency, or pulse duration increases the amount of inhibition of dorsal horn neurons produced by TENS. In addition, the effects of TENS on dorsal horn cells are short lasting, returning to normal after removal of TENS. Similarly, increasing intensity of stimulation to activate Ad fibers increases the inhibition of the flexion reflex with either low- or high-frequency stimulation parameters (Sjolund, 1985, 1988). This suggests that high-frequency TENS is more effective than low-frequency TENS, increasing intensity increases inhibition, and the effects of TENS are short lasting. However, these recordings were done on normal cells and possibly do not reflect effects after central sensitization has occurred. Following carrageenan paw inflammation, wide dynamic range and high threshold dorsal horn neurons sensitize to innocuous and noxious stimuli (Hylden, Nahin, Traub, & Dubner, 1989) and C-fiber evoked responses (Nam, Song, Kim, Baik, & Paik, 1992). This sensitization to innocuous and noxious stimuli is reduced by high- and low-frequency TENS at high/motor intensity (Ma & Sluka, in press) and to C-fiber evoked responses by high-frequency TENS at high/noxious intensity (Nam et al.). The inhibition by TENS is longer lasting than on normal cells, outlasting the time of stimulation (Ma & Sluka; Nam et al.). In a rat model of peripheral neuropathy induced by tight ligation of L5 and L6 spinal nerves, low-frequency, high/motor intensity TENS reduces the enhanced responses of wide dynamic range neurons for up to 90 minutes after TENS (Leem, Park, & Paik, 1995). Thus, TENS reduces innocuous and noxious evoked responses in central neurons in normal animals and after tissue injury.

To test for the role of opioids in TENS antihyperalgesia, the effects of spinal administration of naloxone at doses that block m opioid receptors, naltrindole at doses that block d opioid receptors and nor-BNI at doses that block k opioid receptors prior to application of TENS were examined in the kaolin and carrageenan model of knee joint inflammation. Secondary heat hyperalgesia of the paw was used as the outcome measure because TENS completely reverses this hyperalgesia (Sluka, Deacon, Stibal, Strissel, & Terpstra, 1999). Blockade of m opioid receptors in the spinal cord prevents the antihyperalgesia produced by low-frequency TENS (at sensory intensity) but not high-frequency TENS (at sensory intensity). In contrast, blockade of d opioid receptors in the spinal cord prevents the antihyperalgesia produced by high-frequency TENS but not low-frequency TENS (Sluka et al., 1999). Blockade of spinal k opioid receptors has no effect on either high- or low-frequency TENS antihyperalgesia (Sluka et al., 1999).

The release of endogenous opioids in the spinal cord in response to TENS stimulation could result from activation of local circuits within the spinal cord or from activation of descending inhibitory pathways. The most likely pathway involved in opioid analgesia originates in the periaqueductal gray and sends projections to the rostral ventral medulla (RVM) (Fields & Basbaum, 1994). Neurons in the RVM then project to the spinal dorsal horn. Activation of this pathway produces opioid analgesia and is responsible for the actions of systemically applied morphine (Fields & Basbaum, 1994). Several studies support a role of descending inhibitory pathways in TENS analgesia. Electrical stimulation-induced antinociception is significantly enhanced by administration of L-5-hydroxytryptophan, a serotonin (5-HT) precursor and abolished by the opiate receptor antagonist, naloxone and 5-HT receptor blocker, methysergide (Shimizu, Kojima, Fujisaki, & Fukuda, 1981). Depletion of 5-HT, a neurotransmitter of the raphe-spinal pathway, reduces the antinociceptive effect of high-frequency stimulation in the intact but not in the spinal animal (Woolf, Mitchell, & Barrett, 1980). Microinjection of naloxone at doses that block m opioid receptors, but not that of saline or naltrindole, in the RVM block low-frequency TENS antihyperalgesic effects (Kalra, Urban, & Sluka, 2001). High-frequency TENS antihyperalgesia is blocked by naltrindole, which blocks d opioid receptors, but not by naloxone or saline, microinjected into the RVM (Kalra et al.). Thus low-frequency TENS activates m opioid receptors in the spinal cord and RVM and high-frequency TENS activates d opioid receptors in the spinal cord and RVM.

If TENS is opioid mediated it may follow that it would be less effective for morphine-tolerant patients. In fact, Solomon, Viernstein, and Long (1980) demonstrated that patients who had taken enough opioids to produce tolerance also were tolerant to TENS. However,

stimulation parameters were not given. In rats made tolerant to morphine, low-frequency TENS was less effective at reducing secondary heat hyperalgesia when compared with placebo controls following knee joint inflammation (Sluka, Judge, McColley, Reveiz, & Taylor, 2000). However high-frequency TENS was still equally effective at reducing secondary heat hyperalgesia when compared with placebo controls (Sluka et al., 2000).

TENS is non-invasive, inexpensive, and safe and easy to use. TENS alone may not provide complete inhibition of hyperalgesia and pain and so will probably not be the only method used clinically for pain relief. However, as an adjunct to existing pain relief methods, TENS may have several benefits. Several studies show the intake of opioid analgesics is reduced in patients using TENS (Ghonomie et al., 1999; Rosenberg, Curtis, & Bourke, 1978; Smith, Lewith, & Machin, 1983; Solomon et al., 1980; Wang et al., 1998). Further, systemic morphine (0.3–3 mg/kg) administered alone or in combination with high- or low-frequency TENS, following carrageenan paw inflammation in rats, shifts the dose response curve to the left. This indicates that a lower dose of morphine is now more effective when given in combination with TENS (Sluka, 2000). Reducing opioid intake would be expected to decrease side effects produced by systemic opioids. In fact, high-frequency TENS treatment reduces nausea, dizziness, and pruritis associated with morphine intake compared with morphine alone or sham TENS in postoperative patients (Wang et al., 1997). Further, increasing pain relief by TENS in combination with other therapies will allow the patient the ability to increase activity level and thus reduce hospital stays and speed the return to work. Treatment with TENS increases joint function in patients with arthritis (Abelson, Langley, Vlieg, & Wigley, 1983; Kumar & Redford, 1982; Mannheimer & Carlsson, 1979; Mannheimer et al., 1978; Zizic et al., 1995), decreases the stay in the recovery room in patients following thoracic surgery (Warfield, Skein, & Frank, 1985), increases pulmonary function (measured as vital capacity, functional residual capacity, and arterial PO<sub>2</sub>) (Ali, Yaffe, & Sessle, 1981), and improves the physical and mental component summary on the quality of life survey short form (SF-36) in patients with chronic low back pain (Ghonomie et al., 1999). Thus, several studies support a decrease in opioid intake, a decrease in side effects of opioids, and an increase in a variety of functional tests in patients using TENS. Improving physical function allows the patient to tolerate other therapies and activities resulting in an improved quality of life.

## **Conclusion**

There are several clinical considerations that can be concluded based on the work presented in this review. Use of TENS for referred pain or secondary hyperalgesia should be more effective than use for primary hyperalgesia, particularly for conditions with significant central sensitization. Use of TENS in combination with morphine produces a greater reduction in primary hyperalgesia, should reduce the dosage of morphine necessary to reduce hyperalgesia, and thus decrease side effects of morphine. Low-frequency TENS should not be used if tolerance to morphine is present. However, high-frequency TENS should still be effective if tolerance to morphine is present. Future clinical studies are needed to confirm many of the reports using animal models.

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