

Endorphins and Analgesia Produced by Peripheral Conditioning Stimulation

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Recently, peripheral conditioning electrical stimulation has become a standard procedure to relieve chronic pain in humans. This therapy emerged from the gate theory of Melzack and Wall (24), in which the activity in coarse mechanoreceptive afferents was supposed to presynaptically inhibit the activity of thin nociceptive afferents in the dorsal horn. The experimental data underlying this theory have been criticized (see 27), but nevertheless dorsal horn neurons activated by nociceptive unmyelinated afferents have been reported to be inhibited by stimulation of coarse myelinated fibers (14). Furthermore, the reports on the clinically useful analgesia induced by high-frequency electrical stimulation of peripheral nerves (transcutaneous nerve stimulation, TNS; Fig. 1, *top*) are now many (e.g., 18,19,28,33). However, only 12 to 40% of the patients find the analgesia from the conditioning stimulation sufficient to continue to use it as their main analgesic agent on a long-term basis (18,19).

ACUPUNCTURE-LIKE TNS

To improve the results of treatment with peripheral conditioning stimulation, we have utilized experiences from the Chinese electroacupuncture. With this modification of the ancient acupuncture, the inserted needles are not manipulated but instead high-intensity electrical pulses are delivered at a low rate via the needles (1,16; Fig. 1, *middle trace*). Acupuncture treatment may allow surgery (16), and a rise in tooth pain threshold in healthy volunteers has been observed (1,6,23). However, the method appears to be of limited value in chronic pain (2,12).

Chiang et al. (7) claimed that impulses from deep afferents were necessary to elicit acupuncture analgesia. Andersson and co-workers (1,3; *this volume*) found that a stimulation strength giving forceful muscle contractions in the facial musculature was necessary for the rise in tooth pain threshold. They also found that the pain threshold increase was induced even more readily with stimulation via surface electrodes than via needles, probably because the surface electrodes allowed more current to be passed (1).

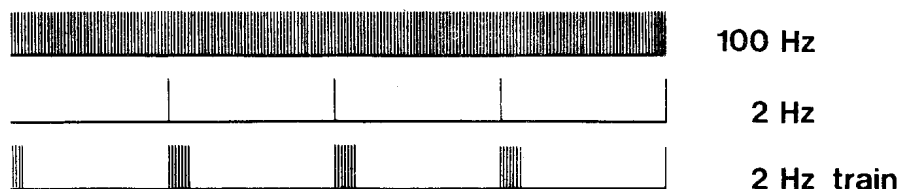


FIG. 1. Different kinds of peripheral conditioning stimulation for induction of analgesia. *Top*, conventional high-frequency TNS (100 Hz); *middle*, electroacupuncture (2 Hz); *bottom*, acupuncture-like low-frequency TNS (2 Hz train).

The failure of electroacupuncture to give sufficient analgesia when tested on chronic pain patients might likewise have been due to the inability to tolerate the high stimulation intensity necessary (2). To overcome this difficulty we have introduced a stimulation of muscle nerves with short trains of monophasic pulses (internal frequency 100 Hz; duration 70 ms) given at a low frequency (2 Hz; Fig. 1, *bottom trace*) via standard TNS electrodes (10). This type of stimulation, acupuncture-like low-frequency TNS, reduced the current necessary to elicit muscle contractions to half or two-thirds of the single shock values and was tried whenever our chronic pain patients did not experience analgesia from conventional high-frequency TNS. The compiled long-term results of stimulation treatment were then improved by about 40% (10,11).

INFLUENCE OF NALOXONE

The opiate antagonist naloxone (20) has been of great value when investigating the pharmacological actions of opiates. In spite of the findings of endogenous opiate receptors (17) and endogenous ligands to these receptors, the enkephalins (15) and the endorphins (13), few if any biological actions have been reported of naloxone in healthy volunteers (9,21; see, however, 4). On the other hand, when administered in double-blind fashion to humans treated with classic needle acupuncture, naloxone partly reversed the induced pain threshold increase (2,23). Therefore we gave volunteer patients treated with acupuncture-like TNS or chronic pain 0.4 to 0.8 mg naloxone under double-blind conditions in pilot experiments and found that three out of the five patients systematically experienced inhibition of their pain relief (29).

We have now extended our study to 10 patients treated with acupuncture-like (lo-)TNS and 10 patients treated with conventional (hi-)TNS (31). All the patients had received their treatment for at least 3 months with portable stimulators (CEFAR S III), experiencing 50 to 100% pain relief as scored on a visual analogue scale (25). Usually the patients were tested with two injections of up to 1.6 mg naloxone i.v., and if experiencing inhibition of the pain relief from stimulation, a double-blind experiment was performed with 4 to 8 injections at 30-min intervals, sterile saline being used as a placebo. The pain intensity was scored on a visual analogue scale 10 min after each injection. All the

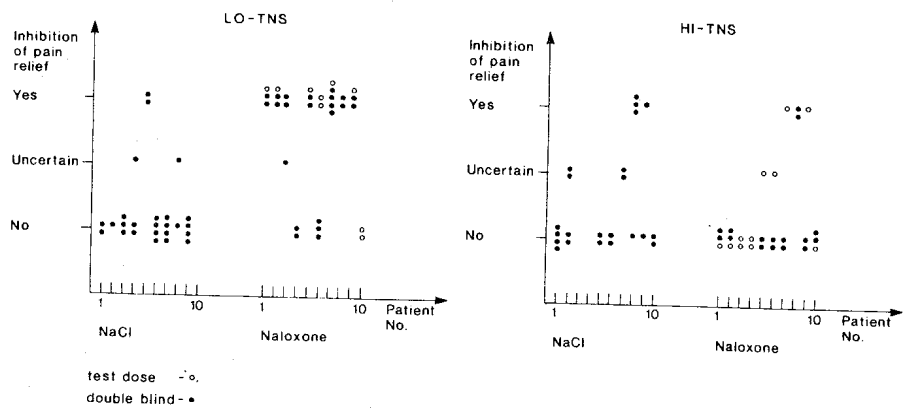


FIG. 2. Influence of naloxone on analgesia from acupuncture-like (LO-)TNS (left diagram) and on analgesia from conventional (HI-)TNS (right diagram). Reactions to saline given separately. Patients within the two groups numbered 1-10. Inhibition of pain relief considered uncertain if less change than 10% of total length of visual analogue scale. Symbols according to key (left).

patients reporting no change in pain intensity received at least two injections of 1.6 mg naloxone i.v. before the observations were considered valid.

From Fig. 2 (left diagram) it can be seen that 6 of the 10 patients receiving lo-TNS specifically experienced inhibition of pain relief from naloxone whereas none of the patients receiving hi-TNS (right diagram) did so. One of the patients in each series reported an inhibition of the pain relief to both naloxone and saline injections, indicating the participation of unrelated factors.

From the present results it thus seems as if the acupuncture-like (lo-)TNS acts through links utilizing endorphins whereas conventional (hi-)TNS produces analgesia via some other mechanism. The interpretation relating to acupuncture-like TNS is in accord with the findings on experimental pain in man (5,22,23) and in mice (26). The inability of naloxone to influence analgesia from conventional TNS, on the other hand, is at variance with the observations of Woolf et al. (34) who reported a reversal of the inhibition of a nociceptive reflex in rats from conventional TNS with naloxone administration. This effect could not, however, be repeated in a different experimental model, employing acute pain in humans (35).

ENDORPHIN MEASUREMENTS

Terenius and Wahlström (32) have developed a method to determine the concentration of two endorphin fractions (I and II) in human cerebrospinal fluid. They then found that the concentration of fraction I was low in patients with trigeminal neuralgia as compared with that in patients without pain. This has later been confirmed in patients with other types of chronic somatic pain (30; Terenius, *this volume*) and might be due to a hypoactivity in the endorphin

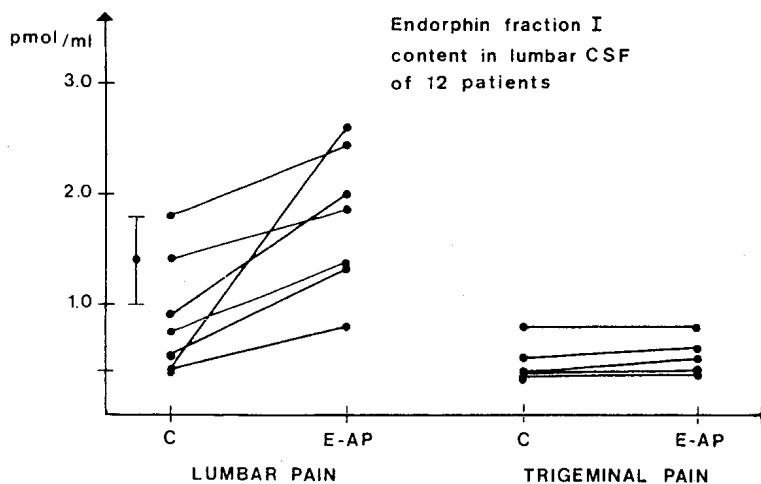


Fig. 3. Endorphin fraction I content in lumbar CSF of 12 patients while experiencing pain (control) and after acupuncture-like TNS (E-AP, electroacupuncture). Content expressed picomoles of met-enkephalin/ml. To the left is given mean \pm SE in patients with no pain.

stems of these patients (32) or to a high consumption of the endorphins released (0).

When the concentrations of these endorphin fractions were measured in the cerebrospinal fluid of our chronic patients before (Fig. 3, C) and after (Fig. 3, AP) acupuncture-like TNS, there was a systematic increase of the fraction concentration in lumbar cerebrospinal fluid of those patients receiving stimulation of lumbar afferents (30 and *unpublished*; Fig. 3). This confirms the results of naloxone administration and in addition points to a local release and action of the endorphins at the spinal level during acupuncture-like TNS (see 8, 36). With conventional TNS, no increase of endorphin concentrations has been seen in pilot experiments (L. Terenius, *personal communication*).

CONCLUSIONS

To combat chronic pain, the central nervous system appears to possess at least two systems that can be influenced independently from the periphery. At least one of them seems to utilize endorphins for this purpose.

ACKNOWLEDGMENT

We would like to acknowledge support of Thorsten and Elsa Segerfalk's Foundation, Sweden.

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