
Transcutaneous Electrical Stimulation With Limoge Current Potentiates Morphine Analgesia and Attenuates Opiate Abstinence Syndrome

Marc Auriacombe, Jean Tignol, Michel Le Moal, and Louis Stinus

Transcutaneous electrostimulation is a somewhat controversial technique used in the management of the opiate withdrawal syndrome. We report an animal study of a particular transcutaneous electrostimulation called transcutaneous cranial electrostimulation, based on a technique used for many years on heroin addicts for the rapid severance of their addiction, which has been validated in a clinical setting by a double-blind trial. This technique involves the application of an intermittent high-frequency current (Limoge's current). Our experimental data show that this transcutaneous cranial electrostimulation increases morphine analgesia by threefold on the tail flick latency measure and produces a 48% attenuation of the abstinence syndrome observed after abrupt cessation of morphine administration. These results were obtained using a double-blind paradigm.

Introduction

The efficacy of transcutaneous electrostimulation to decrease the pain threshold and attenuate the opiate abstinence syndrome has been reported in a number of animal and human studies. Unfortunately, most of the human studies published in the 70s suffer from a lack of rigorous control conditions. Their interpretation has been criticized (reviewed in Whitehead 1978), or they have been thought to have little clinical utility for detoxification of addicted patients (Tennant 1977; Men and Chuang 1980; Gossop et al 1984). However, recent animal studies support the older idea (Choy et al 1978; Ho et al 1978; Ng et al 1975) that transcutaneous electrostimulation attenuates the opiate abstinence syndrome (Malin et al 1988), and has an analgesic effect after nociceptive stimulation (Skolnick 1987). These effects were reported to be mediated by endogenous opioid mechanisms (Malin et al 1988). Thus, study of transcutaneous electrostimulation has both fundamental and clinical implications. Our group has successfully used an original transcutaneous electrostimulation called transcutaneous cranial electrostimulation (TCES) for the rapid attenuation of the opiate abstinence syndrome in humans (Daulouède et al 1980; Ellison et al 1987). Compared to usual low-frequency transcutaneous electrostimulation,

From Inserm U. 259, Université de Bordeaux II, Domaine de Carreire (M.A., M.L.M., L.S.); and Service Universitaire de Psychiatrie, Hôpital Charles Perrons (M.A., J.T.), Bordeaux Cedex, France.

Address reprint requests to Dr. L. Stinus, Inserm U. 259, Université de Bordeaux II, Domaine de Carreire rue Camille Saint Saëns, 33077 Bordeaux Cedex, France.

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TCES is original in that it is a high-frequency intermittent current, which is asymptomatic in humans, allowing long-term application (several days). This clinical experience prompted us to investigate the mechanisms involved in an animal model. The present studies were designed to examine the effect of TCES in two animal models: a measure of tail flick latency (TFL) after nociceptive challenge (D'Amour and Smith 1941) and the abstinence syndrome after chronic opiate intoxication. TCES was carried out using an electrostimulation apparatus designed initially for the potentiation of pharmaceutical anesthesia (electro-pharmaceutical anesthesia) without cutaneous sensation over prolonged periods (Limoge 1975; Limoge and Boisgontier 1979). We report that TCES potentiates morphine-induced analgesia, and attenuates the withdrawal syndrome in morphine-dependent rats. Some of these data have already been presented as abstracts (International Narcotic Research Conference, Albi, France, July 1988).

Methods

The subjects were male Sprague-Dawley rats weighing from 300 to 350 g at the time of testing. Rats were maintained on ad libitum food and water and a 7:00 AM-7:00 PM light-dark cycle. Under chloral anesthesia (chloral hydrate 150 mg/kg IP) three silver disc electrodes (6 mm diameter, 0.3 mm thick) were affixed to each rat: the frontal electrode was placed under the skin between the eyes on the metopic suture and the two posterior electrodes were placed under the skin behind the ears on each side. They were connected to a micro-plug fixed on the calvarium with acrylic cement and four stainless steel screws. TCES was delivered by an electric generator (model ANESTHELEC, MPO3 from COTEC Co, Mérignac, France) delivering in a high-frequency (HF), intermittent, bidirectional, balanced current. The HF 166 kHz was applied for 4 μ sec. The resulting modulated HF output was biphasic, asymmetrical, and the average intensity was zero, which completely eliminated electrode burns due to electrolysis. The 100 mA peak-to-peak stimulation corresponds to 17.5 mCb/sec (17.5 mA effective current). One may consider that the frontal electrode was connected to the negative pole of the generator as it received the negative impulse of weak intensity 33 mA (long duration 4 μ sec) and that the two posterior electrodes were connected to the positive pole as they received the positive impulse of high intensity 67 mA (short duration 2 μ sec) (Limoge and Boisgontier 1979; Barritault et al 1984). During application of TCES, rats were placed in transparent plastic cages with a grid floor; they had free access to food and water. The micro-plug was connected to the stimulator through a mercury contact in order to facilitate the rats' movements, and allow stimulation for hours or days without disturbing the animal.

Potentiation of Morphine Analgesia

Preliminary experiments had shown that TCES alone did not induce analgesia as measured by TFL, but it produced a dramatic potentiation of morphine analgesia related to both the intensity of the current and the dose of morphine (Stinus et al 1989). A total of 21 rats were studied, and each received TFL on three occasions: once with TCES and twice without TCES. The 21 rats received morphine once a week for a period of 3 weeks. This interval was chosen for reasons of tolerance. In a preliminary experiment, the analgesic effect of morphine as measured by TFL was not found to be statistically different after the second and third injection. On the second week, half of the rats received TCES prior

to morphine and TFL testing and the other half received TCES prior to the third episode of TFL testing. Experimental and control animals were distributed without the knowledge of the experimenters, and measures of TFL were made by an experimenter ignorant of the identity of the subjects. In the comparison of TFL, rats were used as their own controls in order to reduce interindividual variability in sensitivity to morphine. Morphine chloride was administered at a dose of 10 mg/kg subcutaneously. TCES started 3 hr before morphine injection and was maintained continuously for 9 hr.

TCES Effects on Opiate Withdrawal

Opiate withdrawal was studied with 20 morphine-dependent rats. Rats received IP injections of morphine twice a day according to the following design: 5 mg/kg the first day, 10 mg/kg the second, and then increasing by 10 mg/kg per day to attain a dose of 90 mg/kg per injection on the 10th day. The last IP injection of morphine occurred on the morning of the 11th day. The rats were then placed in cages for TCES, which started 3 hr later and lasted 4 days. The control (nonstimulated) group was also connected to the stimulator but no stimulation was delivered. Here again, control and experimental rats were distributed randomly, and the behavioral management was identical. Rats were observed during periods of 5 min each, three to four times a day during 3 days for measurement of opiate withdrawal symptoms according to a modified version of Gellert's scale (Gellert and Hoitzman 1978): wet dog shakes, facial fasciculation, teeth chattering, swallowing movement, ptosis. Three measures were also videotaped for control ratings by an experimenter blind to the subject's status. Each rat received a withdrawal syndrome rating three times on the first and third day (9:00 AM, 2:00 PM, 5:30 PM, and 9:00 AM, 2:30 PM, 7:00 PM, respectively) and four times on the second day (9:00 AM, 2:00 PM, 6:30 PM, and 10:30 PM).

Results

Potentiation of Morphine Analgesia

Treatment with morphine alone increased TFL for 3 hr after the injection with a peak at 1 hr. TCES was found to potentiate this morphine analgesia (Figure 1a). Analysis of variance (ANOVA) revealed a significant group effect [$F(1,20) = 188, p < 0.001$] showing that analgesia was statistically different between stimulated and control conditions. The overall time course of the morphine-induced analgesia was not changed by TCES. The effect of the stimulation was almost immediate, and 1 hr after morphine injection, TFL was 3 times that observed in the control group. Figure 1b shows individual results for the 21 rats. TFL measured with morphine alone is shown on the X axis, and the increase in TFL observed with TCES is plotted on the Y axis. All the animals appeared to exhibit increased morphine effects after TCES.

Attenuation of Opiate Withdrawal

The overall time course of the score obtained on Gellert's scale was used as an index of withdrawal (Figure 2). The syndrome lasted for at least 3 days with a peak on the third day. TCES did not change the time course but considerably reduced the intensity of the syndrome and the peak, which occurred earlier at the end of the second day.

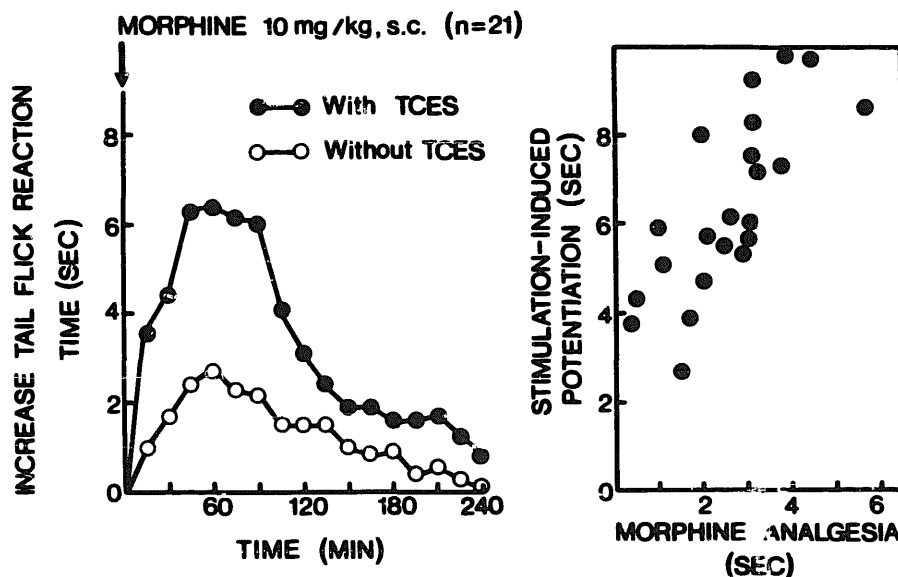


Figure 1. Potentiation of morphine analgesia by TCES as measure by the increase in TFL after nociceptive challenge. All rats received 10 mg/kg SC injection of morphine chlorhydrate. TCES started 3 hr before morphine injection and continued for 9 hr. (a) Overall results for experimental animals (with stimulations) and controls (without stimulation) $p < 0.001$; (b) individual results showing the increase in TFL produced by TCES.

The total mean score for the 3 days was 4.64 for the control rats and 2.52 for the stimulated rats (-46%). ANOVA revealed a significant group effect [$F(1,18) = 24.2$, $p < 0.0001$] showing that withdrawal scores were statistically different between stimulated and control animals. The individual scores computed as the mean of the three highest scores obtained by each subject during the 3 days of observation are represented in Figure 3. The mean score for an individual in the control group was 8.73, whereas in the stimulated group it was 4.53 (-48%). ANOVA revealed a significant group effect [$F(1,18) = 47.6$, $p < 0.0001$].

Discussion

The aim of these studies was to demonstrate a direct effect of TCES in two experimental situations: morphine-induced analgesia and the abstinence syndrome from morphine in the rat. The former was significantly increased and the latter was reduced by TCES. The effects were highly significant especially with respect to the intensity rather than the duration of action. The results were obtained using paradigms designed to eliminate observation bias or experimentation artefacts.

The present animal investigation was based on a special technique used successfully for many years in clinical practice by our group. The apparatus used for this study is regularly used in the management of the withdrawal syndrome in human narcotic addicts. It has been found to alleviate the aversive symptoms resulting from opiate abstinence, enabling management of addiction in combination with other long-term treatments such as psychotherapy (Daulouède et al 1980; Daubech et al 1981). Contrary to other types of transcutaneous electrical stimulation, it has been validated in a double-blind clinical study (Ellison et al 1987). This technique was initially used in anesthesiology (Cara et

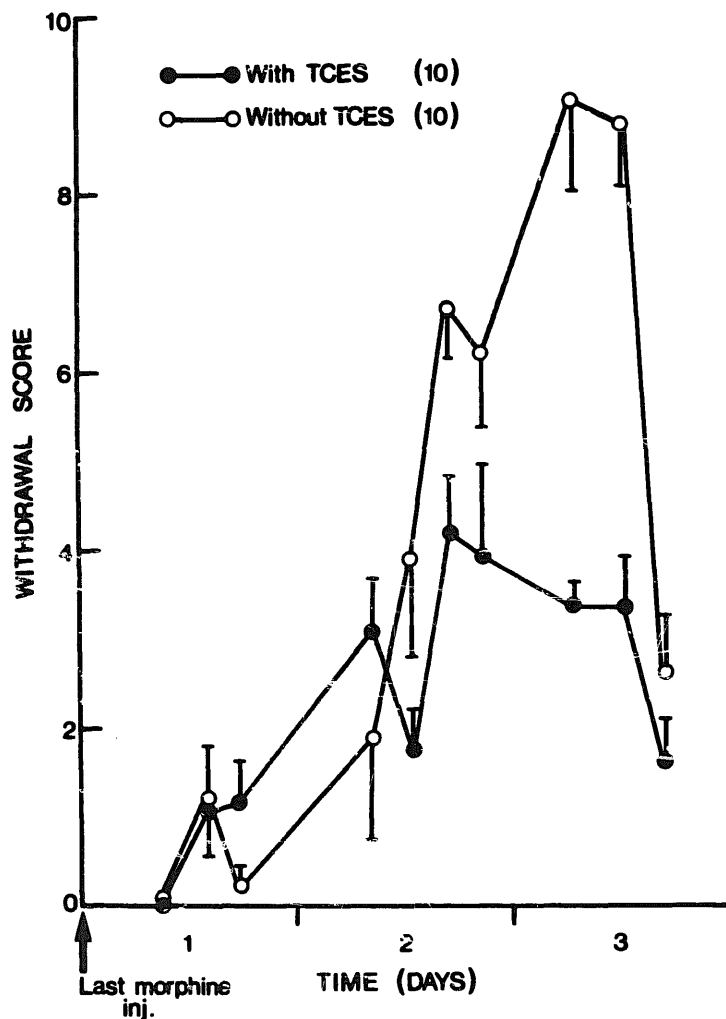


Figure 2. Attenuation of morphine withdrawal by TCES (overall results). Withdrawal is scored by Gellert's scale. TCES started 3 hr after last exposure to morphine. Mean score is 2.52 for experimental group (with TCES) and 4.64 for controls (without TCES) $p < 0.0001$. Note that the study extends over 3 days.

al 1972), where it has been reported to potentiate anesthetics and opiates, prolonging the duration of preoperative and postoperative analgesia (Stanley et al 1982; Boudallé-Badie et al 1980).

The complex current used for TCES was developed for human use by Limoge and co-workers, and it is free of adverse reactions, allowing long-term treatment (Limoge 1975; Limoge and Boisgontier 1979; Barritault et al 1984). It is original in that it associates a high-frequency intermittent current with a low-frequency current. Thus, it is asymptomatic and allows long-term application (several days) of high-intensity current.

The other types of transcutaneous electrostimulation are essentially combined with acupuncture (electroacupuncture) or auricular acupuncture (auricular electroacupuncture) and use a low-frequency current of low or very low intensity for short periods of time (a few minutes); these currents are based on the acupuncture paradigm. These techniques

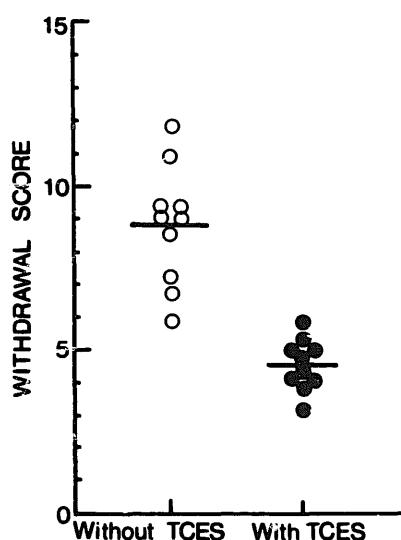


Figure 3. Attenuation of morphine withdrawal by TCES. Individual results computed as the mean of the three highest scores obtained during the 3 days. Withdrawal is scored on Gellert's scale. Mean score for experimental group (with TCES) 4.53, and for controls (without TCES) 8.78, $p < 0.0001$.

have not been clinically validated on the bases of double-blind trials. The seminal study of Wen and Cheung (1973) has been criticized. Whitehead (1978), in a review and analysis of the literature, concluded that the utility of acupuncture alone or associated with electrical stimulation remained unproven clinically, mainly due to lack of rigorous methodological controls. Nonetheless, in animal studies, it has been shown that transauricular electrostimulation could suppress, for a short time, the naloxone-induced morphine withdrawal syndrome in the rat (Ng et al 1975) and mouse (Choy et al 1978; Ho et al 1978), which is correlated with an elevation of brain opiate-like activity (Ho et al 1978) and with a concomitant suppression of plasma adrenocorticotropin (ACTH) (Choy et al 1978). More detailed investigations have been published recently (Malin et al 1988; Skolnick et al 1987) demonstrating that auricular microelectrostimulation increases TFL after nociceptive challenge and attenuates the opiate abstinence syndrome in rats. This effect was thought to be mediated by the endogenous opioid system (Malin et al 1988).

There is a discrepancy between animal and clinical studies in the response to transcutaneous electrical stimulation but not for TCES (Limoge's current) this could be due to the presence of the unique combination of low- and high-frequency current which allows long-term application. Using different paradigms, our results confirm and extend these recent data. Further clinical and fundamental studies are required to evaluate this technique, which appears to be safe, efficacious, and potentially useful.

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