doi:10.1111/j.1355-6215.2006.00020.x

Suppression of cue-induced heroin craving and cue-reactivity by single-trial transcutaneous electrical nerve stimulation at 2 Hz

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ABSTRACT

The purpose of the present study was to investigate the efficacy of 2 Hz transcutaneous electrical nerve stimulation (TENS) to reduce cue-induced heroin craving and the corresponding cardiovascular responses. Seventy heroin addicts with at least 1 month of abstinence were enrolled and randomly divided into two groups of 35, to receive single-trial 2 Hz TENS (TENS group) or mock TENS (mock group) during experimental procedure, respectively. They were required to express their degree of craving by visual analog scale before and after the presentation of a video-cue, and after TENS treatment, which lasted for 30 minutes. Heart rate and arterial blood pressure were simultaneously monitored in 56 cases, with 28 in each group. Results show that in mock group, video-cue induced a dramatic increase of craving score, which did not return to baseline in 150 minutes, whereas in the TENS group, 2 Hz TENS treatment produced a significant decrease of craving, reaching baseline in 90 minutes. Video-cue induced a significant increase of heart rate and systolic and diastolic blood pressure, which remained elevated for at least 60 minutes in the mock group; whereas in the TENS group, they returned to baseline immediately after the termination of TENS. These results indicate that the craving induced by a heroin-related cue can be immediately and significantly suppressed, and the cardiovascular activation totally abolished by a single-trial 2 Hz TENS for 30 minutes

Keywords Cue reactivity, drug-related cue, heroin craving, heroin dependence, relapse, transcutaneous electrical nerve stimulation.

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INTRODUCTION

It is well known that clinical treatment of opiate addiction includes at least two aspects: the detoxification and the prevention of relapse. While the former can be effectively resolved by various measures, the latter remains a hard task for clinicians and researchers. Gossop *et al*. (1989) reported that the average abstinence time for opiate addicts after in-patient treatment program was only 25 days, and 3 months after the treatment the percentage of those who were still abstinent was only 5%, suggesting that when compared with detoxification, relapse prevention is much less effective in being treated. Opioid agonists and antagonists are among the most popularly used medications. Methadone maintenance (Kleber 2003) has been regarded as the most effective treatment for this purpose, although prolonged use of methadone itself will inevitably result in its dependence. Naltrexone is a specific opiate antagonist with pharmacological effects lasting longer than 24 hours and has therefore been proposed for the treatment of heroin addiction (Van Ree 1996). Yet its potential damage to liver function (Jiang *et al*. 1999; but see also Brewer & Wong 2004) raises major concerns regarding its prolonged use. Besides, the existence of protracted withdrawal syndromes during the treatment period results in a low patient compliancy. Of course, there are many other methods used to prevent relapse including psychotherapy (Rounsaville, Carroll & Back 2005), acupuncture (Han, Trachtenberg & Lowinson 2005) and the recently introduced cue exposure treatment (Franken *et al*. 1999).

Relapse to drug use can be triggered by exposure to the drug, by situations previously associated with drug taking or by exposure to stressors (Self & Nestler 1998;

Shalev, Grimm & Shaham 2002). In this context, conditioned stimuli seem to play a critical role (Gawin 1991; Drummond 2000). Craving, a strong subjective desire to use the drug of choice, is believed to contribute to the occurrence of relapse. Cue-reactivity refers to a classical conditioned response that occurs when an addicted subject is exposed to drug-related stimuli. This response is presumed to consist of physiological and behavioral reactions.

Transcutaneous electrical nerve stimulation (TENS) is a peripheral electrical stimulation (PES) provided via electrodes placed on the skin. Recent findings have shown that PES in specific frequencies applied to certain body sites corresponding to traditional acupuncture therapy can facilitate the release of specific neuropeptides in the central nerve system, eliciting profound physiological effects and clinical implications (Han 2003). Our previous studies have demonstrated that 2 Hz TENS applied on certain acupoints could ameliorate withdrawal syndromes in human heroin addicts and postpone relapse of drug use (Wu, Cui & Han 1995a,b), reducing heroin craving as measured by visual analog scale (VAS) (Han *et al.* 2005). As those results were obtained via long-term observations or at least assessed 24 hours after the TENS treatment, no data are available on whether TENS has an immediate effect on reducing the craving induced by a heroin-related cue, being one of the most important factors leading to relapse. So the present experiment was designed to observe the effect of 2 Hz TENS on cue-induced craving. While the determination of the degree of craving relies on VAS, a subjective measure, we tried to use some objective measures (heart rate and blood pressure) in this study to validate the effect of TENS in the suppression of craving.

MATERIALS AND METHODS

Subjects

Seventy heroin-addicted persons undergoing detoxification in an in-patient program unit (Ankang Mental Health Care, Beijing, China) were recruited and randomly and evenly divided into two groups of 35. All participants had abstained from heroin use for a minimum of 1 month and a maximum of 6 months. The heroin-dependent subjects were identified in accordance with Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) criteria (American Psychiatric Association 1994) and none of them scored positive on a urine drug test, when recruited for the present study. Candidates were excluded from the study, if one of the following conditions arose: acute withdrawal symptoms, hypertension, affective disorders, intellectual disability and significant somatic disorders. This sample consisted of 50 males and 20 females and their mean age was 27 years and 4 months (SD = 5.1 years). Subjects had on average a previous history of 5 years of heroin use (SD = 2.81 years) and had attempted detoxification at least twice before. The study was approved by the Ethical Committee of the Peking University and the AnKang Mental Health Care, where the work was performed. All subjects participated voluntarily, providing written informed consents.

Procedure and assessments

2 Hz TENS

Transcutaneous electrical nerve stimulation was provided by the programmed pulse generator 'Han's acupoint nerve stimulator' (HANS) model LH-202. The device was produced by the Hua Wei Company, Beijing, China, generating a constant current square wave output via two pairs of skin electrodes for a total of 30 minutes. Four skin sites (acupoints) were stimulated: the Hegu (LI 4, at the midpoint of the second metacarpal bone on the radial side) and Laogong (PC 8, midway between the second and third metacarpal bones on the palmar side, where one's middle finger falls when one makes a fist) of the left hand, and Neiguan (PC 6, 2 inches above the palm, between the palmaris longus and flexor carpi radialis tendon) and Waiguan (SJ 5, 2 inches above the skin crease on the back of the wrist, between the ulnar and radius) of the right forearm. The frequency of stimulation was 2 Hz, and pulse width 0.6 milliseconds. The intensity (constant current output) of the stimulation was set so as to increase stepwise to determine the threshold value, which was in the range of 4–6 mA, and then doubled to reach a level of 8–12 mA. They were encouraged to take a stronger stimulation if it did not produce any unpleasant feeling. The highest level used was 15 mA. A mock device of identical appearance was used for those subjects randomly appointed to the control group, with the output of the device being locked at 5 mA. The display on the LCD screen could be increased by the operator to the level of 12 mA, yet the real output remained at the threshold level.

Cue

Video-cue was used in this experiment, showing two male heroin addicts, who were inhaling heroin. The duration of the video presentation was 3 minutes.

Measurement of craving

A single-item self-rating scale (Powell 1995) was used to assess the intensity of craving before and after the presentation of the video-cue, and after the termination of the single-trial 2 Hz TENS (or the mock TENS) which lasted for 30 minutes. The VAS ranged from 0 (no craving) to 100 mm (strongest possible craving). For the purposes of the present study, craving was defined as the strength of

the attraction to use drugs. The degree of craving was presented as percentage form.

Measurement of cue-reactivity

Cue-reactivity included heart rate and arterial blood pressure (systolic and diastolic). They were recorded by a wrist blood pressure meter (model EW3032, Panasonic, Japan). The unit of heart rate was per minute, and the unit of arterial blood pressure was mmHg (Carter & Tiffany 1999).

Procedure of experiment

Initial recordings of baseline level of craving, heart rate, systolic and diastolic blood pressure were taken after a resting period of 5 minutes. Subjects were then exposed to the heroin-related video for 3 minutes, after which the same recordings were repeated. They were then administrated with single-trial 2 Hz TENS (or mock TENS) for 30 minutes. After that the recordings were repeated at 30-minute intervals for two (cardiovascular) to five (craving) times, when the relevant parameters were returned to the baseline level for more than 30 minutes in the TENS group.

Data analysis

Data were processed by the commercially available software Graphpad Prism 4.0. All the data (degree of craving, heart rate and arterial blood pressure) were shown as mean ± SEM. Comparison between two groups was analyzed with a two-way analysis of variance (ANOVA) followed by Bonferroni post-tests. The accepted level of statistical significance was a *P*-value of less than 0.05.

RESULTS

Clinical records of heroin abstinents in the mock and 2 Hz TENS group

Validated clinical information of subjects is shown in Table 1. The mock group had an average age of 27.83 ± 5.84 years, which was not significantly different from that of the 2 Hz TENS group of 27.20 ± 0.95 ($P > 0.05$). There was no significant difference in gender distribution ($P > 0.05$) between the two groups. The quantity of heroin used per day was 0.99 ± 0.09 g and 1.07 ± 0.11 g in the mock and 2 Hz TENS group, respectively ($P > 0.05$). Further, there was no significant difference between the two groups concerning the years of abuse and duration of abstinence ($P > 0.05$).

Inhibitory effects of single-trial TENS at 2 Hz on craving induced by heroin-related video

Figure 1 shows that in the mock TENS group, heroin craving score increased from 39.20 ± 3.31% to 67.94 ± 3.42% in response to the video-cue. Corresponding

Table 1 Clinical records of heroin addicts in the mock and 2 Hz TENS group.

	Mock group	*2 Hz TENS group*
Age, years	27.83 ± 0.99	27.20 ± 0.95
Gender, *n* (%)		
Male	25 (71.43)	25 (71.43)
Female	10 (28.57)	10 (28.57)
Drug intake mode, *n* (%)		
Inhale	11 (31.43)	13 (37.14)
Injection	24 (68.57)	22 (62.86)
Drug intake per day, g	0.99 ± 0.09	1.07 ± 0.11
Time of drug use, years	5.24 ± 0.6	6.63 ± 0.75
Duration of abstinence, months	1.76 ± 0.19	1.64 ± 0.15

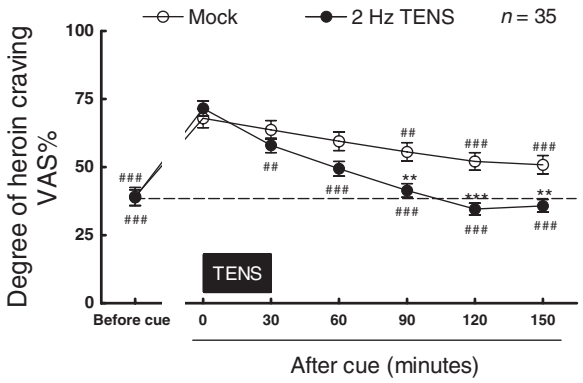

Figure 1 The effect of 2 Hz transcutaneous electrical nerve stimulation (TENS) on the degree of heroin craving induced by video-cue. ○, mock TENS group; ●, 2 Hz TENS group. Shown are mean ± SEM. $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$, compared with the degree of craving measured immediately after cue exposure in each group. $^{**}P < 0.01$, $^{***}P < 0.001$, compared with mock TENS group. Two-way ANOVA followed by Bonferroni *post hoc* tests. The broken line represents the baseline level of craving in the 2 Hz TENS group before cue exposure. VAS = visual analog scale

scores in the 2 Hz TENS group were 38.86 ± 2.87% and 71.91 ± 2.78%, respectively. It is evident that in both groups there was a marked increase in craving following the video-cue ($P < 0.001$, compared with the score before the cue). In the mock TENS group, at the termination of a single trial of mock TENS for 30 minutes, the degree of craving fell slightly from 67.94 ± 3.42% to 63.74 ± 3.38%, which was not significantly lower than the score before the treatment. A progressive and significant decrease occurred at the time points of 90, 120 and 150 minutes ($P < 0.01$, $P < 0.001$, compared with the score before mock TENS), but still significantly higher than that before cue presentation ($P < 0.001$, $P < 0.01$, $P < 0.05$). In the 2 Hz TENS group, however, the craving score decreased to 58.03 ± 2.62% immediately after the termination of the TENS ($P < 0.01$, compared with the pre-TENS value), and then decreased further to

49.43 ± 2.69% at the 60 minutes time point, returning to the baseline level at the 90 minutes time point and even lower than the baseline level at the time point of 120 minutes (34.63 ± 2.18%). The difference between the real TENS group and the mock TENS group after the treatment was very significant ($P < 0.01$, $F = 3.555$). These results imply that 2 Hz TENS for 30 minutes produce immediate and significant inhibitory effects on heroin-related video-cue-induced craving.

Inhibitory effects of single-trial 2 Hz TENS on the cue-induced increase of heart rate

Figure 2 shows that in the mock TENS group, exposure to a heroin-related cue produced an increase in heart rate from 71.6 ± 1.9/minute to 78.9 ± 2.0/minute ($P < 0.05$), remaining at a high level for at least 60 minutes ($P > 0.05$, compared with the heart rate immediately after cue). A similar degree of cue-induced increase in heart rate was observed in the 2 Hz TENS group, from 71.1 ± 1.8/minute to 78.9 ± 2.0/minute ($P < 0.01$). However, at the termination of the 2 Hz TENS, heart rate went down to baseline level (70.0 ± 1.7/minute), remaining at the baseline level thereafter. The difference between the mock TENS group and 2 Hz TENS group was statistically significant ($P < 0.05$, $F = 5.306$), indicating that 2 Hz TENS for 30 minutes resulted in an immediate abolishment of the cue-induced increase in heart rate.

Inhibitory effects of single-trial TENS at 2 Hz on the cue-induced increase of systolic blood pressure

Figure 3 shows that in the mock TENS group, the heroine-related video-cue produced an increase in systolic blood pressure from 114.8 ± 1.9 mmHg to 124.9 ± 1.9 mmHg ($P < 0.001$). Similar changes were observed in the 2 Hz TENS group, an increase from 115.3 ± 1.5 mmHg to 123.6 ± 1.7 mmHg ($P < 0.01$). A single-trial mock 2 Hz TENS for 30 minutes produced no significant decrease in systolic pressure within 60 minutes. In contrast, the 2 Hz TENS group displayed a significant decrease in systolic blood pressure down to 115.5 ± 1.6 mmHg to reach the baseline level and remained at the same level thereafter ($P < 0.01$, compared with the pre-TENS value). In other words, the 2 Hz TENS for 30 minutes abolished the hypertensive effect induced by video-cue ($P < 0.05$, $F = 6.31$ versus mock group).

Inhibitory effects of single-trial TENS at 2 Hz on the cue-induced increase of diastolic blood pressure

Figure 4 shows that the video-cue induced a significant increase of diastolic blood pressure from 74.6 ± 1.6 mmHg to 82.9 ± 1.6 mmHg ($P < 0.001$) in the mock TENS group, and a similar change from 75.0 ± 1.5 mmHg to 82.3 ± 1.4 mmHg ($P < 0.01$) in the 2 Hz TENS group. A single-trial mock 2 Hz TENS for 30 minutes produced no significant decrease of diastolic pressure, which remained at a high level within 60 minutes. In contrast, the 2 Hz TENS produced a sharp drop in the diastolic blood pressure to the baseline level (74.3 ± 1.7 mmHg) and remained low thereafter (74.5 ± 1.5 mmHg). The difference between the mock TENS group and 2 Hz TENS group is statistically significant ($P < 0.05$, $F = 6.215$).

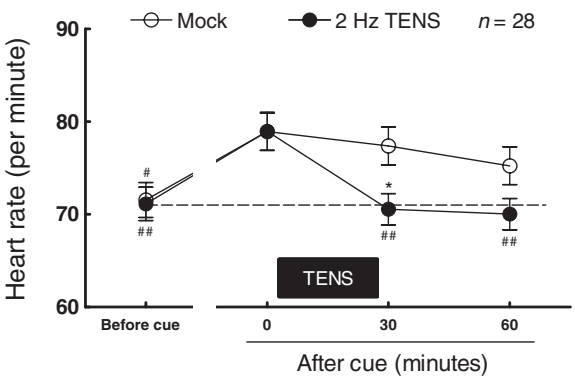

Figure 2 Increase of the heart rate produced by video-cue and the effect of 2 Hz transcutaneous electrical nerve stimulation (TENS) on heart rate. ○, mock TENS group; ●, 2 Hz TENS group. Shown are mean ± SEM. $^{\#}P < 0.01$, $^{\#\#}P < 0.01$, compared with the data measured immediately after cue exposure in each group. $^{*}P < 0.05$, compared with the mock TENS group. Two-way ANOVA followed by Bonferroni *post hoc* tests. The broken line represents the baseline level of the cardiovascular parameter in the 2 Hz TENS group before cue exposure

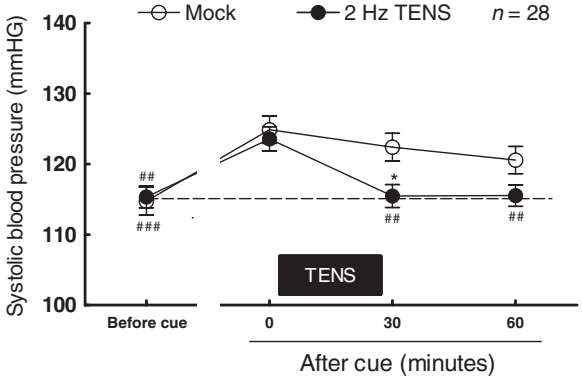

Figure 3 Increase of the systolic blood pressure produced by video-cue and the reduction of blood pressure by 2 Hz transcutaneous electrical nerve stimulation (TENS). ○, mock TENS group; ●, 2 Hz TENS group. Shown are mean ± SEM. $^{\#}P < 0.01$, $^{\#\#}P < 0.01$, compared with the data measured immediately after cue exposure in each group. $^{*}P < 0.05$, compared with the mock TENS group. Two-way ANOVA followed by Bonferroni *post hoc* tests. The broken line represents the baseline level of the cardiovascular parameter in the 2 Hz TENS group before cue exposure

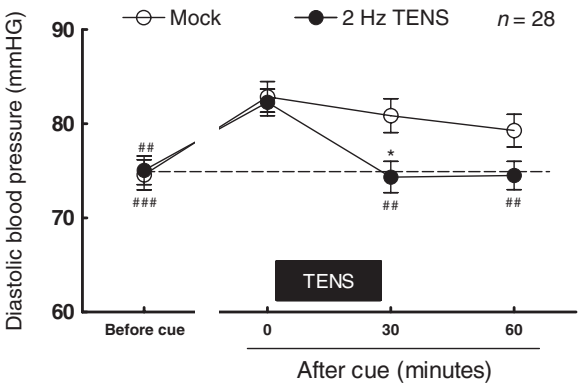

Figure 4 Increase of the diastolic blood pressure produced by video-cue and the reduction of blood pressure by 2 Hz transcutaneous electrical nerve stimulation (TENS). ○, mock TENS group; ●, 2 Hz TENS group. Shown are mean ± SEM. $^{\#}P < 0.01$, $^{\#\#}P < 0.01$, compared with the data measured immediately after cue exposure in each group. $^{*}P < 0.05$, compared with the mock TENS group. Two-way ANOVA followed by Bonferroni *post hoc* tests. The broken line represents the baseline level of the cardiovascular parameter in the 2 Hz TENS group before cue exposure

DISCUSSION

In recent years, a consensus has been reached that craving as an intense desire for drugs of abuse can trigger an increased motivation in drug-seeking (heroin, morphine or others) and drug-taking behavior. In other words, the role of craving is invoked as the primary motivating force behind relapse (Childress, McLellan & O'Brien 1986). Parallel to the subjectivity of craving, there are objective responses that occur, when an addicted person is exposed to drug-related stimuli, referred to as cues. These responses consist of physiological reactions, e.g. changes of blood pressure and heart rate. While cue is the general expression for the entire stimuli, e.g. exteroceptive, interoceptive or temporal, the most commonly studied cues are exteroceptive, such as sight, smell or taste. A syringe used for drug administration is a typical cue to induce craving and relapse to drug use, possibly through a cue-reactivity mechanism (Powell *et al*. 1990, Powell, Gray & Bradley 1993; Childress *et al*. 1993; Weinstein *et al*. 1997; Carter & Tiffany 1999). The video used in the present study was taken from a typical environment of heroin use, which is a much stronger cue as compared with a syringe. It is interesting to note the similarity between these two reactions in the mock TENS control groups, as seen in Fig. 1 (craving) on the one hand and the other three figures (cardiovascular responses) on the other, both reactions remaining at the high level for at least 60 minutes. However, one can find a significant difference in these two reactions, i.e. a single-trial 2 Hz TENS for 30 minutes produced a complete abolishment of the cardiovascular response, whereas the degree of craving did not return to the baseline level until 60 minutes after the termination of TENS. The rapid response of the cardiovascular manifestation to PES seen in the present study is consistent with our previous findings that the acute withdrawal syndromes of the heroine addicts could be significantly suppressed by TENS within minutes. Continuous recording of heart rate revealed that a statistically significant decrease of heart rate occurred within 10 minutes, with a maximal effect appearing within 20 minutes and remaining at the plateau until the termination of the 30-minute stimulation (Wu, Cui & Han 1996). A powerful suppression of psychic arousal (craving) and the complete abolishment of physical arousal (sympathetic activation) would certainly be of extreme importance at this critical situation, which would otherwise lead to relapse of drug taking.

The mechanisms underlying the inhibitory effect of TENS on craving and cue-reactivity induced by a heroin-related video are not yet clear. Wang *et al*. (2000) reported that 2 Hz PES inhibited morphine-induced conditioned place preference (CPP) in rats by increasing the release of endogenous opioid peptides, most likely enkephalin, to interact with mu and delta opioid receptors in a naloxone-reversible manner. The 2 Hz PES could also abolish the stress- and drug priming-induced reinstatement of extinguished CPP in the rat, which was also naloxone-reversible (Wang *et al*. 2003). As the long-term abstinence of opiates in opioid-dependent subjects would inevitably lead to the sensitization of the opioid receptors, a physiologically accessible increase of opioid peptides would be strong enough to reduce craving and ameliorate CPP.

Besides the opioid effect, there were also some non-opioid substances such as dopamine, norepinephrine and serotonin, being released in the central nervous system during TENS stimulation (Han 1993). It has been shown that central catecholamine and serotonin play key roles in mediating the analgesic effect of acupuncture (Han 1993). As pain is among the most serious symptoms of withdrawal syndrome, suppression of pain would certainly be beneficial for blocking the relapse of drug taking. The potential role played by these substrates in the anti-craving effect of TENS is not yet clear. In a recent review, Hall *et al*. (2004) pointed out that while dopamine is an important neurotransmitter for reward, it is not the sole determinant. For example, cocaine CPP can still be developed in mice with the deletion of dopamine transporters. In contrast, cocaine CPP was totally abolished in mice with a double knockout of the dopamine transporter and serotonin transporter. The results suggest that the interactions between several monoamines are necessary for the mediation of cocaine reward. Whether this applies for morphine or heroin addiction still needs to be elucidated.

In conclusion, a heroin-related video-cue induced an abrupt increase of heroine craving lasting for several

hours, as well as resulting in an increase of heart rate and blood pressure lasting for at least 1 hour. These reactions can be completely abolished (cardiovascular) or dramatically suppressed (craving) by 2 Hz TENS within 30 minutes. The results suggest that TENS can be used as an effective measure for the prevention of relapse to heroin abuse.

Acknowledgement

This work was supported by a grant from the National Natural Science Foundation of China (30170814) to L.Z.W., and a grant from the National Basic Research Program (2003-CB515407) of China to L.Z.W. and J.S.H.

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