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REVIEW

Acupuncture-related techniques for the treatment of opiate addiction: a case of translational medicine

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Abstract **Drug addiction is a chronic brain disorder characterized by withdrawal symptoms that occur during drug abstinence and a high tendency of relapse. Compared with the currently available pharmacological interventions, acupuncture therapy has the potential to help drug addicts stay away from drugs without major adverse side effects. It has taken decades of research to optimize the parameters of electrical acupoint stimulation for detoxification and for relapse prevention, as well as to establish a safe and easy procedure by which drug addicts can use it on themselves. The discovery that acupuncture can trigger the release of opioid substances from the brain in the 1970s provided the inspiration. Following this, basic research on animals made it possible to understand the mechanisms of action and establish the procedure for treating drug addictions. This article reviews the past, present, and foreseeable future regarding the use of acupuncture-related technique for the treatment of opiate addiction from the perspective of translational medicine.**

Keywords morphine; dependence; withdrawal; addiction; dynorphins; acupuncture; electroacupuncture; transcutaneous electrical acupoint stimulation (TEAS); enkephalins; endorphins

Introduction

Drug addiction is a major social problem in many countries including China. Opiates comprise one of the most commonly abused drugs [1,2]. The most popular method currently available for the treatment of opiate addiction is pharmacological intervention, a popular example of which is the methadone maintenance treatment (MMT) [3]. MMT is a replacement therapy using long-acting opiates to fulfill the bodily needs of the addict, thereby shifting the homeostasis from a natural baseline level to an elevated level (opioid saturation). However, it is a great challenge to bypass pharmacological measures to help the opiate addicts get rid of the drugs and stay drug-free without suffering. In this article, we review a translational study that attempts to apply acupuncture-related techniques to help opiate addicts end drug abuse using the two-step procedure of detoxification followed by relapse prevention.

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Why acupuncture treatment is effective for drug addiction

Historical review

Although acupuncture has been used in China for thousands of years, using it for the treatment of drug addiction began with a serendipitous discovery by H. L. Wen, a neurosurgeon in Hong Kong [4]. Dr. Wen once intended to treat a heroin addict with cingulotomy under acupuncture anesthesia. The technique required 30 min of acupuncture stimulation prior to the surgical procedure. In less than 30 min, the patient said that his withdrawal symptoms disappeared, and there was no need for subsequent surgery. Similar cases occurred several times, which prompted Dr. Wen to start a clinical trial. Dr. Wen found from his study that acupuncture alone was capable of partially removing the withdrawal symptoms produced by heroin abstinence. The technique used by Dr. Wen was as follows: four needles were inserted into the right hand (IL 4 and SI 3) and the arm (EH 4 and TB 9), and two other needles were inserted into the right ear points of brain stem and shenmen. An electrical stimulator was used for half an hour.

In 1974, Wen and Cheung's acupuncture protocol was

adopted by the Lincoln Recovery Center in Bronx, New York with two modifications: (1) acupuncture was applied only on the ear, with five needles inserted bilaterally into the outer ear or auricule of ear points of kidney (CO $_{10}$), liver (CO $_{12}$), lung (CO $_{14}$), shenmen (TF $_{4}$) and sympathetic (AH $_{6a}$); and (2) the electric stimulation was omitted. The protocol was reported to be effective across different substances of abuse. In 1985, under the guidance of Dr. Michael Smith, the Director of the Detoxification Center, the National Acupuncture Detoxification Association (NADA) was formed and the five-point auricular protocol (now known widely as the "NADA protocol") was codified. The NADA protocol was later used in many clinics in Western countries, including residential programs, acute detoxification facilities, and outpatient programs [5].

In a recent international conference held in Hong Kong from January 14–16, 2011, Dr. M. Smith delivered a speech entitled "Ear Acupuncture Protocol Meets Global Needs" [6]. He stated that the NADA protocol was used in the public health model and there were no diagnostic procedures. Generally, a 3- to 5-point protocol was most effective for the patients to become more clear-headed and comfortable. Today, nearly 1000 licensed drug treatment programs use acupuncture in the US. It is used in 130 prisons in England, UK, and many refugee camps worldwide.

Research on acupuncture analgesia

We started our research on the acupuncture-induced analgesic effect in 1965 to look for possible mechanisms behind the clinical phenomenon of "acupuncture anesthesia" [7,8]. It was this concept, which was considered novel at that time, that inspired Dr. Wen to use acupuncture for cranial operations in Hong Kong. In a laboratory setting in Beijing Medical College, medical student volunteers were assessed for their skin pain threshold with the potassium iontophoresis method [7]. We intended to know whether acupuncture applied at one point of the body would cause an increase in pain threshold over the whole body. The results showed that mechanical twisting of the needle inserted into the skin of the acupoint located at the thenar eminence of the hand produced a general increase of the pain threshold over the whole body. The effect had a slow onset and reached a plateau in 30 min. When the needle was removed from the body, the pain threshold started to decline with a half-life of about 16 min. This pattern of pain threshold change was later shown to be reproducible not only in humans, but also in animals, including rodents, rabbits, dogs, and monkeys [9].

In later studies, we used an electrical stimulator connected to the needles to deliver electrical pulses to the acupuncture sites in lieu of mechanical stimulation. This was entitled as electro-acupuncture (EA). EA produces analgesic effects that are almost identical to those of manual needling, with the added advantage of precision in terms of pulse frequency, intensity and pulse widths; reproducibility; and less need for manpower [10,11]. This is especially suited for laboratory research. The finding that the analgesic effects of both manual acupuncture and EA are sensitive to naloxone blockades suggests that they might be mediated by endogenous opioid substances through opioid receptors [12]. Further research demonstrated that the release of endogenous opioid peptides is frequency-dependent: low frequency (2 Hz) triggers the release of enkephalins from the central nervous system to interact with μ opioid receptors, and high frequency (100 Hz) stimulation causes the release of dynorphin from the spinal cord to interact with κ opioid receptors. Activation of both the μ and κ receptors can produce analgesic effects [13]. Although there was no such term as "translational medicine" in the 1980s, applying basic research findings to clinical practice was always desired by basic research scientists. A portable electrical device, entitled the Han's Acupoint Nerve Stimulator (HANS), was introduced to clinical practice in the late 1980s to enhance the effects of acupuncture anesthesia and was met with considerable success [13].

In the year 1990, according to a report, China had 70 000 heroin addicts, most of whom are in the south-west border area. What could we do to help? If EA can promote the release of opioid peptides to produce an analgesic effect, it would be natural to expect the same approach being effective in treating heroin addicts in order to reduce their withdrawal syndromes.

Preliminary animal experiments

An animal model was established by repeated injections of morphine into rats for 5 days. An injection of the opioid receptor antagonist naloxone precipitated serious withdrawal syndrome, suggesting that the rats were successfully made dependent on morphine. The withdrawal symptoms were significantly reduced by EA administered to the hind limbs. The effect was much greater with high frequency (100 Hz) compared with that induced by low-frequency (2 Hz) EA [14]. This was unexpected since opioid dependence was thought to be related with the μ-opioid system rather than the κ-opioid system. Thus, we went to the clinic to test the effect of HANS for the treatment of withdrawal syndrome in heroin addicts.

Preliminary human studies

A problem was encountered when applying EA to drug addicts: they were irritated by needle insertion. In extreme cases, the needle inserted into the acupoint was sometimes broken from excessive agitation. For patient safety, as well as ease of use, metal needles were replaced by self-adhesive electrodes placed on the skin over the acupoints. Experimental data showed that this transcutaneous electrical acupoint stimulation (TEAS) was at least as effective as EA, if not more effective [15]. With the HANS unit, the

frequency of electrical stimulation can be selected as 2, 100, or 2/100 Hz (2 Hz and 100 Hz alternating every 3 s). The latter was also called dense-and-disperse (DD) mode of stimulation. Studies revealed that while 2 and 100 Hz stimulation individually increased the release of enkephalin and dynorphin, respectively, the DD mode increased the release of both enkephalin and dynorphin simultaneously to produce a synergistic effect [16,17]. This frequency is most effective in pain control [18] and in the control of opiate withdrawal [19].

Detoxification

Among the spectra of withdrawal syndromes, we chose the following easily detectable objective signs: heart rate, bodyweight, and the sparing effect of opioid subscription, such as methadone and buprenorphine.

Heart rate

Following an abrupt opioid abstinence, the heart rate of heroin addicts increased dramatically to as high as 100–120 beats per minute (BPM), and remained above 90 BPM for as long as 7 days. A single treatment with HANS at DD (2/100 Hz) mode for 30 min reduced the heart rate significantly. The effect peaked (~90 BPM) in 20 min. However, this effect was short lived, and the heart rate returned to original levels within 30 min after the termination of HANS treatment [20]. If HANS was administered once a day for 10 days, the heart rate was brought back to lower than 80 BPM in 4 days and remained low thereafter. Similar effects were observed with either 2 Hz or 100 Hz stimulation, with DD mode being the most effective, followed by 100 Hz and then 2 Hz [21]. These results on humans agreed with the findings observed in rats, that 100 Hz was more effective than 2 Hz, while DD mode produced the best results.

Bodyweight

Heroin addicts generally have very low bodyweight, with an average of 50 kg (212 cases, age: 15–38, M/F: 3.2/1). The bodyweight of the three HANS-treated groups significantly increased, starting from day 5 and peaking on day 10, with an average increase of 4.5–5.0 kg ($P < 0.01$). The bodyweight of the control group remained low for the entire 10-day duration of drug abstinence [21]. The increase of bodyweight observed in the HANS treated groups was apparently due to decreased withdrawal syndrome and increased food and water intake. No difference was observed between the three HANS-treated groups at frequencies 2, 100 and 2/100 Hz, suggesting that the mechanisms of action underlying the heart rate change and bodyweight modulation may not be the same.

Sparing of opioid subscription

To obtain a quantitative estimate of the effects of HANS, a clinical trial was carried out in a voluntary detoxification center. The basic treatment was buprenorphin (BPN, i.m.). The patient was allowed as much BPN as they liked when they experienced withdrawal syndrome. In all, 28 patients were randomly divided into 2 groups. One group used BPN only, while the other group was provided with HANS treatments in combination with BPN. A 4-channel HANS (8 electrodes) was used instead of the 2-channel device. HANS treatment was administered 3–4 times a day in the first 5 days, followed by 2 times a day for 5 days, and then once a day for the last 4 days. The amount of BPN used in the course of the 14-day treatment was taken as the primary end point. The results showed that the total amount of BPN used in the HANS group was only 8% of that in the BPN-only group, which was used mainly in the first 5 days. This result represented an accumulation of the therapeutic effects produced by repetitive HANS treatments in the 14-day period [22]. Similar results were observed in a different group of heroin-addicted patients using methadone as a control and HANS (2/100 Hz) in conjunction with methadone as the experimental group. The total dose of methadone used in the HANS group was only 25% of that used in the control group [23].

These trials, published between 1993 and 2001, were open trials without blinding for the observers; therefore, they should be viewed only as preliminary studies.

Relapse prevention

After the successful detoxification, the former heroin addicts were allowed to return to their homes. However, within six months, most of them went back to drugs. The annual relapse rate could be as high as 97%–98% [24]. In the US and UK, relapse occurs in most cases within days after detoxification [25,26]. Relapse had multiple causes, the most prominent of which are the protracted withdrawal syndrome (negative reinforcement) [27] and the intense drug craving (positive reinforcement) [28].

The effect of TEAS on suppression of craving

In a rehabilitation center, 171 former heroin addicts were recruited, all of whom had completed their detoxification process at least one month ago. The visual analog scale (VAS, 10 cm full scale) was employed to simulate the degree of craving. Subjects with a basal degree of craving lower than 2.0 were dismissed. The assessment was performed once a day for 30 consecutive days. Results obtained from the first 10 days and the last 10 days were taken as pre-control and post-control values, respectively, and those from the middle 10 days were taken to evaluate the effect of TEAS on craving. The subjects were randomly divided into 4 groups, and 3 of them were given TEAS of 2, 100 and 2/100 Hz, respectively, for 30 min a day just after the measurement of craving. Another group was given mock TEAS, with barely sensible current at 15 Hz for 3 min, which was then switched off. The results showed that in all 4 groups, there was a general

tendency of slow reduction of the craving. In the mock TEAS group, the slope remained stable during the whole period of observation. The 100 Hz group showed a small increase in slope in the TEAS treatment period without statistical significance. In contrast, the 2 Hz group and the 2/100 Hz group showed a sharp increase in slope, suggesting a significant lowering of the craving with considerable after effects. The conclusion is that for the suppression of craving, 2 Hz or 2/100 Hz TEAS was significantly more effective than 100 Hz TEAS [29,30].

The effect of TEAS on preventing relapse to heroin use

Preliminary clinical trials were executed in several cities throughout China. The first was in Haikou City in the Hainan Province of southern China. A rehabilitation center was established under the supervision of the Neuroscience Research Institute of Peking University, using TEAS as the main method of intervention for the heroin addicts. The staff kept close contact with the former heroin addicts discharged from the detoxification center. They were allowed TEAS treatment every day for free. Using monthly urine tests as outcome criterion, the relapse rates at 3, 6, 9, and 12 months were 50.0%, 71.4%, 80.4% and 83.9%, respectively. Those showing 12-month consecutive negative urine tests were given an injection of 0.4 mg of naloxone. A null response to naloxone challenge further confirmed their heroin-free status. Considering the literature report of 94% relapse rate at 6 months and more than 98% at one year for heroin users following detoxification, the success rate of over 16% in one year in our series is quite encouraging [30].

Another clinical trial took place in Shanghai, in which a total of 164 previous heroin addicts aged 18–52 were recruited. They had experienced compulsory isolation for anywhere from 3 months to as long as 3 years. The criteria for recruitment included the following: (1) the patient must be discharged from the detoxification center no more than one year ago, still with protracted withdrawal syndrome and willing to be in the treatment and observation program; and (2) the patient must undergo an opiate-free urine test (thin layer chromatograph). The participants were provided with a 2-channel HANS unit. They were asked to treat themselves 3 times a day in the first month, twice a day in the second month, and at least once a day (before going to sleep) in the third month, followed by 1–2 times a week for the rest of the year. Weekly consultation was provided by social workers to ensure the correct use of the device and to help solve other relevant problems. Urine was checked once a month without prior notice. For those showing positive urinalysis, a second test was performed within a week. A second positive test would result in the termination of the observation, which was marked as a failure. At the end of the observation period, 35 patients showed 12 consecutive negative urine tests, which were then counted as success. However, 76 dropped out for different reasons, and these were all counted as relapses. The one-year success rate was 32.3%, the highest success rate ever reported so far. An attempt was made trying to correlate the relapse rate with the compulsory isolation period to check whether or not longer isolation would result in a higher success rate. No such correlation was revealed, suggesting that a longer isolation after detoxification did not help prevent relapse [31]. The pitfall of this study was the lack of a control group due to the failed approval of the ethical committee. The idea was that if a person was assigned to a mock HANS group, he or she may become a victim of this assignment owing to the otherwise-preventable relapse to the drug.

Further studies on detoxification

Searching for optimal conditions for suppressing withdrawal syndrome in the rat

We have shown that single trial of 100 Hz EA (30 min) can effectively suppress withdrawal syndrome in the rat [32,33]. However, it remained obscure if multiple sessions of EA would strengthen the effect, and how often should it be used for maximal alleviation of opiate withdrawal syndrome.

It has been documented that too many EA treatments a day would result in a gradual decrease of the analgesic effect, leading to EA tolerance [34]. However, it is not clear as to how many sessions of EA treatment should be given to drug addicts in order to produce maximal suppression of opiate withdrawal syndrome without the occurrence of tolerance. An experiment was performed in the rat [35]. Morphine dependence was induced by subcutaneous injections of morphine twice daily for 10 days with increasing dosage (10, 20, 40, 80, 120 mg/kg). Rats made tolerant to and dependent on morphine were divided into 4 groups receiving 0, 1, 2, and 4 sessions of 100 Hz EA, respectively, each lasting for 30 min. Spontaneous withdrawal syndrome was assessed 24 and 60 h after the last EA session. Observation of naloxone-precipitated withdrawal syndrome was made 7 days after the termination of EA. The results showed that first, 100 Hz EA suppressed the withdrawal syndrome, and multiple sessions of EA were more effective than a single session, with the after-effects lasting for as long as 7 days. Second, a downregulation of preprodynorphin (PPD) mRNA levels was observed in the spinal cord, peri-aqueductal grey (PAG), and hypothalamus 60 h after the last morphine injection, which could be reversed by multiple sessions, but not a single session of 100 Hz EA. Third, accompanied by the decrease of PPD mRNA levels, there was an upregulation of p-CREB in the three CNS regions, which was abolished by 100 Hz EA treatment. These findings were interpreted to mean that a downregulation of p-CREB and acceleration of dynorphin synthesis in the spinal cord, PAG, and hypothalamus may be implicated in the cumulative effect of multiple 100 Hz EA treatments for opiate detoxification. Fourth,

accompanied by the reduction of withdrawal syndrome, there was an increase in the effect of EA analgesia in the multiple EA group, which naturally became beneficial for reducing pain and suffering. Overall, the results suggested that during the period of severe withdrawal syndrome, 2–4 sessions of EA a day may be appropriate for the amelioration of withdrawal syndrome, with after effects lasting for as long as 7 days [35].

Similar findings have been obtained by electron microscope observation of neurons in the ventral tegmental area (VTA). After 14 days of morphine treatment, the rough endoplasmic reticulum swelled, membrane configuration of the nucleus and mitochondria blurred, and the structure of the myelin sheath changed. Both 2 and 100 Hz EA treatments reversed the morphological alterations induced by chronic morphine administration [36]. Hu *et al*. used electrophysiological measures to assess the sensitivity of the DA neurons in VTA. In normal rats, a small dose (1 mg/kg) of morphine induced increased firing rate of the VTA DA-neurons. Chronic morphine administration decreased the sensitivity of DA neurons to morphine, which can be rescued by 100 Hz EA treatment administered once daily for 10 days [37]. All the data mentioned above suggest that multiple sessions of EA that strengthen the endogenous opioid system are helpful in protecting the CNS from the damaging effect of chronic morphine usage.

Chronic morphine administration also produces functional and morphological alterations in the mesolimbic dopamine system (MLDS), which is believed to be the neurobiological substrate of opiate addiction. A study has been designed to investigate if EA could reverse the cell size reduction induced by chronic morphine treatment in the VTA, an important area of the MLDS [38]. The results showed that first, escalating doses of morphine treatment twice a day for 14 days resulted in a cell size reduction of dopaminergic cells (–44%, 14 days after the last morphine injection) and reduced the number of brain-derived neurotrophic factor (BDNF) cells in the VTA (–29% in 14 days) of the rats. Second, these changes of the DA neurons were site-specific, occurring in the VTA, but not in the adjacent substantia nigra. Third, 100 Hz EA treatment for 13 sessions during the 14-day morphine abstinence period was capable of rescuing the dopaminergic and BDNF cells in the VTA from the damage produced by chronic morphine administration. Fourth, an upregulation of BDNF protein levels in this area by 100 Hz EA may play a role in the repairing of morphological damage of dopaminergic neurons. The results listed above indicate that 100 Hz EA may play an important role in the treatment of opiate withdrawal through the DA system.

Randomized controlled clinical trials using TEAS for opioid detoxification

A randomized controlled clinical trial was performed at the Detoxification Center in Zhongshan City, Guangdong Province in May and June, 2010, to assess the feasibility of using TEAS for the amelioration of withdrawal syndrome occurring in heroin addicts during drug abstinence [39]. In all, 63 male heroin addicts were randomly divided into 2 groups. The HANS group participants (n = 32) were provided with a HANS unit with 2 pairs of outputs connected to 4 self-adhesive skin electrodes 2.9 mm × 2.9 mm in size; these were placed on the four acupoints, Hegu (LI 4) / Laogong (P 8) on one hand and Neiguan (P 6) / Waiguan (TE 5) on the other forearm. Pulsed square waves with alternating positive and negative currents were used to stimulate the LI 4/P 8 and P 6/TE 5, respectively. The frequency was set at the DD (2/100 Hz) mode, and the intensity of the constant current output was set at twice the threshold, i.e., if the threshold level to produce a tingling sensation was 5 mA, then 10 mA would be used for stimulation. Each session lasted for 30 min. The control group participants were given mock HANS, which appeared identical to the verum HANS with the light blinking, but no current was delivered. Three sessions of TEAS per day were used for the first 5 days, followed by 2 sessions per day for the remaining 5 days. Withdrawal syndromes were assessed and recorded twice daily in the morning and evening, using the structured withdrawal questionnaire. Sublingual buprenorphine (BPN) 0.5 mg was used as a rescue when needed. In the mock HANS group the global withdrawal score remained high for the first 4 days and decreased gradually to 50% of the original level by day 10. In contrast, the HANS group showed a sharp drop to 50% on the second day and decreased continuously to 5% of the original level by day 10. Taking the area under the curve (AUC) as an index, the ratio between the mock HANS and HANS groups was 40:17 ($P < 0.001$), suggesting that HANS produced a nearly 60% reduction of overall withdrawal syndrome [39]. From the results of this randomized controlled study, it can be concluded that multiple TEAS treatments for 10 days are effective in reducing withdrawal syndrome in heroin addicts during drug abstinence.

In a recent study using the same HANS device as mentioned above, Mead *et al*. tested the effectiveness of TEAS as an adjunctive treatment for inpatients receiving opioid detoxification with buprenorphine/naloxone at the McLean Hospital in Harvard University [40]. Participants (n = 48) were randomly assigned to the active (constant output intensity of 8–15 mA) or sham (output intensity of 1 mA only) TEAS groups and received three 30-min treatments daily for 3–4 days. Two weeks post-discharge, participants in the active TEAS group were less likely to have used any drugs (35% vs. 77%). They also reported greater improvements in pain control and physical health over time compared with the sham TEAS group. The authors concluded from this pilot study that TEAS is an acceptable, inexpensive adjunctive treatment that is feasible to implement at an inpatient unit and may be a beneficial adjunct to pharmacological treatments for opioid detoxification.

Further studies on relapse prevention

Animal experiments on the suppression of psychic dependence

It is well-known that drug addiction is a chronic, recurrent condition with a rate of relapse as high as 95%–99%. Therefore, the final goal of treating drug addiction is not only to accomplish detoxification (relieving or curing the withdrawal syndrome), but also to relieve craving (psychological dependence) and remove the compulsive behavior of drug seeking and usage after detoxification. There are several animal models [41] that can be used to simulate the drug craving and relapse to drugs, and conditioned place preference (CPP) is one of them.

In a two-chamber experimental apparatus, the drug (unconditioned stimulus) was injected to an animal in one of the chambers, and normal saline in another chamber. After repeated training for 4 times each, the rat will choose to stay longer on the drug-associated side than in a chamber associated with normal saline. The ratio between the times spent in the 2 chambers can be taken as an index for the degree of "craving." Experiments were conducted to test whether acupuncture can suppress the expression of morphine-induced CPP. Wang *et al*. [42] first observed the effect of EA at 2, 100, or 2/100 Hz (DD) on morphine CPP expression in rats. The result showed that the CPP was significantly suppressed by EA of 2 and 2/100 Hz, but not of 100 Hz. These results suggest that it is low-frequency component of the EA mediated by μ and δ receptors that suppresses the CPP expression.

Liang *et al*. [43] further localized the nucleus accumbens (NAc) as the site of action. A single session of 2 Hz EA produced a significant increase of the release and the tissue content of enkephalin in the NAc of morphine-induced CPP rats. This effect was stronger in rats receiving 3 consecutive sessions of EA. These consecutive sessions of 2 Hz EA upregulated the mRNA level of preproenkephalin in the NAc of morphine-induced CPP rats. These findings support the feasibility of using 2 Hz EA for the treatment of opiate addiction.

Although a single session of 100 Hz EA was ineffective in blocking morphine CPP [44], multiple treatments of 100 Hz EA (once a day for 3 days) were effective [45]. This effect can be blocked by the δ- and κ-, but not the μ- opioid antagonists.

In a further study, Chen *et al*. [46] confirmed that the efficacy of EA in suppressing morphine-induced CPP depends not only on the frequency of EA (2 Hz $>$ 100 Hz), but also on the number of EA sessions administered (5 times $>$ 3 times $>$ single session). This may reflect the degree of activation of the genes encoding opioid peptides. By measuring the mRNA level of preproenkephalin (PPE) and preprodynorphin (PPD) in the NAc of morphine CPP rats, 2 and 100 Hz EA were found to selectively elevate PPE and PPD mNRA levels, respectively [47].

Considering that opioids are known to elevate dopamine (DA) activity in the mesolimbic brain, we tried to further analyze the possible involvement of the mesolimbic dopaminergic system (MLDS) in the EA-induced suppression of the rewarding effects of morphine in the rat. The MLDS serves a vital role in pathological behavioral changes occurring with repeated exposure to abusive drugs [48,49]. In the MLDS, dopaminergic neurons originating in the ventral tegmental area (VTA) project to the NAc, a key neural substrate implicated in the rewarding effects of morphine and cocaine [50]. The μ-opioid receptor agonists increase DA release in the NAc by inhibiting GABAergic neurons in the VTA, which provide tonic inhibition of DA neurons, resulting in increased DA release in terminal regions [51]. Thus, the overwhelming actions of DA in the NAc may lead to neural adaptation that underlies the addiction of drugs.

Ma *et al*. [52], meanwhile, explored the effect of EA on the maintenance and the reinstatement of morphine CPP and to determine whether MLDS is involved in the effects of EA. The establishment of morphine-induced CPP is always accompanied by an increase of the tissue content, the turnover rate and the gene expression of the DA neurons in the NAc. On the other hand, EA of 2 Hz or 100 Hz produced a 25%–35% decrease of the contents of DA and its metabolites, DOPAC and HVA, in the NAc of rats compared with those in the control group during the maintenance of morphine-induced CPP.

In real life, craving and relapse can be induced easily by stress or by a very small dose of opioids. This phenomenon can be reproduced in animals using the CPP model. Wang *et al*. [42] reported that morphine-induced CPP disappeared after a 9-day extinction period. The extinguished CPP could be easily reinstated by foot shock stress, or by a small dose of morphine. Again, the reinstated CPP could be reversed by 2 or 2/100 Hz EA in a naloxone-preventable manner [44].

In the rats showing reinstatement of morphine-induced CPP, 3 consecutive sessions of EA (either 2 Hz or 100 Hz) suppressed the reinstated CPP (behavior expression), accompanied by a 40%–50% decrease in the contents of DA and its metabolites, DOPAC and HVA, in the NAc (neurochemical indices) [52].

Taking all the findings into consideration, we can summarize that 3 consecutive sessions of EA produced the following consequences: (1) a suppression of the CPP, which has been previously shown to be naloxone reversible [42]; (2) an increased expression of PPE and PPD [45]; and (3) rescuing the MLDS activation produced by small doses of morphine [50]. What, then, is the internal relationship among the three events (see Fig. 1).

It is rational to postulate that although both 2 and 100 Hz EA produce similar effects of suppressing the CPP, their mechanisms may not be identical. A single session of 100 Hz EA increases the release of dynorphin in the central nervous system [11], while repeated 100 Hz PES further increases the PPD gene expression [45]. An increased release of dynorphin in the NAc can activate presynaptic κ-opioid receptors in the

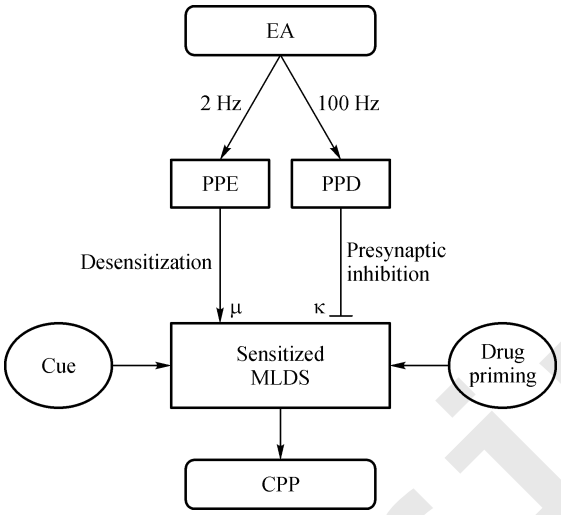

Fig. 1 Diagram showing the cue-induced CPP or drug priming-induced reinstatement of CPP was suppressed by EA of different frequencies. While EA of both 2 Hz and 100 Hz can suppress CPP, the mechanisms of action are not identical. PPE: preproenkephalin, PPD: preprodynorphin. Modified from Ref. 52.

NAc, leading to a presynaptic inhibition of the release of DA in the NAc. This mimics the recent finding that exogenously administered κ-opioid agonists suppressed morphine CPP [53].

Concerning the possible mechanisms underlying the blockade of CPP by 2 Hz EA, the following findings should be taken into account. First, 2 Hz EA stimulation accelerated the central release of enkephalin and endorphin rather than dynorphin [11]. Second, repeated 2 Hz EA augmented the central expression of mRNA encoding PPE [45]. Third, clinical observation indicated that previous heroin addicts on their first 48 h of drug abstinence were very sensitive to drug (one inhalation was enough to produce euphoria) or endogenously released opioid peptides (one session of HANS stimulation often led to a considerable degree of euphoria), suggesting a sensitized state of the MLDS. Based on these findings, one could postulate that abstinence of opiate drug leads to the sensitization of opioid receptors. A slow but continuous release of enkephalin may cause desensitization, resulting in a lowered response of the MLDS to a priming dose of morphine. To this end, a DD mode of stimulation containing both 2 and 100 Hz components might be optimal for the opiate addicts to decrease their craving and withdrawal syndrome, thereby preventing relapse to opiates.

Randomized controlled clinical trial for the prevention of relapse to heroin use

In the Beijing area, we recruited 154 former opioid addicts who were discharged from the detoxification center within 3–6 months and were willing to be treated with TEAS for the prevention of relapse. They were randomly divided into 2 groups. The HANS group members used an active HANS device with 2/100 Hz output at an intensity of 10–15 mA delivered through 2 pairs of skin electrodes placed on the Hegu/Laogong and the Neiguan/Waiguan points. They were trained to use the device at least once daily (up to 3 times a day when needed) under the supervision of social workers. The expected time of treatment was one year. At the beginning of the observation period, the withdrawal syndrome was assessed by structured questionnaire, the degree of depression and anxiety assessed by HAND and HAMA, respectively, and the degree of craving by VAS. These assessments were repeated at the end of the 12-month observation period. Urine tests for morphine were performed once a month at a scheduled time. A successful result was marked by a negative urine test for consecutive 12 months, and the absence of withdrawal signs in response to an injection of naloxone (0.4 mg) at the end of the program. The results showed that all the 76 persons in the mock HANS group showed a positive urine test for morphine at the end of 9 months. At the same time, 48.7% showed negative urinalysis results in the HANS group. At the end of the 12-month observation period, successful results were obtained in 34 cases, constituting 43.6% of the total cases in the HANS group. Meanwhile, there was a significant reduction of craving and withdrawal syndrome in the HANS group compared with the mock HANS group [39].

Cue-induced craving is known to be one of the most significant causes of relapse to drugs. To investigate the effect of TEAS to reduce cue-induced craving and the corresponding cardiovascular responses, Zhong *et al.* [54] studied 70 heroin addicts with at least 1 month of drug abstinence in response to single-trial 2 Hz TEAS ($n = 35$) or mock TEAS ($n = 35$). The standard cue was a 3-min video about the behavioral response to an intravenous injection of heroin in two male drug addicts. The degree of craving was assessed by VAS, and the heart rate and arterial blood pressure were monitored simultaneously. Results showed that in mock group, the video cue induced a dramatic increase of craving score, which did not return to baseline for 150 min; whereas in the TEAS group, 30 min of 2 Hz TEAS treatment produced a significantly less craving which returned to baseline in 90 min. The video cue induced a significant increase in heart rate and systolic and diastolic blood pressure, which persisted for at least 60 min in the mock TEAS group; whereas in the TEAS group, they returned to baseline immediately after TEAS treatment. These results indicate that cue-induced craving can be significantly suppressed, and the cardiovascular symptoms abolished by a single-trial 2 Hz TEAS for 30 min.

Summary

Acupuncture technique continues to evolve over time

Acupuncture as an ancient healing technique has been evolving over time. The tools of acupuncture have changed

from sharp stones in ancient times to thick silver needles and then fine stainless steel needles in modern age. The use of electricity made it possible to apply electrical pulses to needles (EA or TEAS) in lieu of mechanical stimulation. These techniques are called "acupuncture-related techniques (ARTs)." ARTs are easy-to-apply and labor-saving procedures that are highly reproducible and especially suited for laboratory research. EA and TEAS, however, are not intended to replace manual acupuncture; they only serve as an alternative under certain conditions.

Ear acupuncture was less commonly used in ancient times compared with the present time. Modern ear acupuncture is an invention of the French doctor Paul Nogier who, in the early 1950s, stated the somatotopic presentation of the inverted fetus in the ear and named the anatomic regions of the fetus corresponding to specific zones of the ear. Dr. M. Smith has been optimizing the method of acupuncture from Wen's protocol of body and ear acupuncture to ear acupuncture only. Later on, it also changed from a 5-needle to a 3-needle protocol. He even tried to change needle acupuncture to magnetic beads stimulation (personal communication).

It can be expected that acupuncture related techniques will continue to evolve following the advancement of science and technology. Whatever changes would happen, doctors and researchers should strive to (1) describe the technical details as much as possible, (2) scientifically prove the beneficial therapeutic effect of the new technique they are introducing, and (3) try to demonstrate the mechanisms of action along with the clinical practice.

Review of the past research from the view point of translational medicine

Looking back in terms of translations from bench work to bedside to community application, the NADA approach quickly translated firsthand knowledge obtained from bedside to community application, while the Peking University approach put much effort on bench work and the interactions between bench and bedside.

Dr. M. Smith said in his 2011 conference lecture in Hong Kong that although "there are no diagnostic procedures," nor any basic research, the 3- to 5-point ear acupuncture protocol has been applied in more than 1000 licensed drug treatment programs in the world. Most patients liked it because the procedure made them more clear-headed and comfortable. At the same time, the correction officers liked it because there was an 80% reduction of violent incidents in the prison. This is certainly a sound reason justifying continued usage of the treatment.

The research group in Peking University directed their knowledge obtained from basic research on acupuncture-induced analgesia to the new applications for drug addiction alleviation. They started from rat experiment and then tried it on humans. They also extended their knowledge from detoxification (physical dependence) to the prevention of relapse (psychic dependence). They optimized the parameters of EA for the treatment of different stages of drug dependence. Low frequency (represented by 2 Hz) EA is most effective for suppressing the withdrawal syndromes and high frequency (100 Hz) EA is best for alleviating craving. They determined that the low and high alternating frequency (DD mode) is best for both withdrawal syndromes and craving. They studied the possible mechanisms (especially the neurochemical mechanisms) underlying the frequency dependence of the EA treatment. They provided TEAS instead of EA to make it much more acceptable by drug users, thereby paving the road for community application, especially in relapse prevention.

Future research directions

Fighting drug abuse is an endless battle. To best help the victims, both pharmacological and non-pharmacological interventions should be administered to complement each other. The combination of MMT and TEAS is one of the possibilities to consider.

Various kinds of drugs that are being abused are emerging every year. Each has its own characteristics, often requiring extensive research to understand its mechanism of action. For example, in contrast to morphine-induced CPP, which needs 2 Hz EA for effective suppression, an ideal treatment for cocaine-induced CPP requires 100 Hz EA [55]. This may have some implication for future studies. On the other hand, different drugs may act through certain common pathways. Looking for all-in-one solutions by acting on such common pathways, if they exist, is definitely worth studying. Interventions to restore the homeostasis of the body may serve as a general solution.

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