

Acupuncture treatment of drug addiction

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SUMMARY

Acupuncture as a therapeutic intervention has been widely used for treatment for many functional disorders, such as substances abuse and mental dysfunction. In general, acupuncture is known to be simple, economic, painless, non-traumatic, and without untoward reaction, being able to inhibit the abstinence syndrome. Although a number of studies on acupuncture have been reported, a few studies described acupuncture effect on drug addiction. Evidences suggest that substances abuses including nicotine, cocaine and alcohol are in part related to its effects on dopamine neurons in the reward pathways of the brain. The effects of acupuncture on drug addiction may be mediated through the neuronal cells within the limbic structures, which are known to be involved in rewarding properties of drug abuse. This essay reviews clinical and experimental evidences for its effectiveness on the drug addiction, and discusses a plausible explanation for the mechanism of acupuncture on substances abuse.

Key words: Acupuncture; Addiction; Dopamine; Nicotine; Cocaine; Alcohol

INTRODUCTION

The influence of addiction affects a pall across the society, with ramifications extending far beyond the addicted individuals. The nature of addiction makes it extremely difficult to determine its extent, ultimate effects, or the best treatments, and current medications offer only a partial solution (Otto, 2003).

Acupuncture is, together with the use of herbal medicines and other treatment modalities, a major part of traditional Oriental medicine. While acupuncture has been known only recently in the West, its acceptance has increased rapidly (Lee *et al.*, 2004). In 1997, a consensus panel by the National Institutes of Health (NIH) concluded there is clear evidence that needle acupuncture treatment is effective for postoperative and chemotherapy

nausea and vomiting, nausea of pregnancy, and postoperative dental pain. It also concluded there are a number of other conditions for which acupuncture may be effective, including addiction (NIH consensus conference, 1998).

The acupuncture therapy in the treatment of substance abusers and drug withdrawal has been demonstrated to the scientific community. The interest for the use of acupuncture in the treatment of addictions began with Wen and Cheungs work that opium addicts, treated with postsurgical analgesic electroacupuncture, were relived from withdrawal symptoms (Wen and Cheung, 1973). In fact, acupuncture has become standard procedure in many detoxification programs worldwide (Sytinsky and Galebskaya, 1979). However, due to the lack of the number and quality of clinical trials, the efficacy of acupuncture for the addictive disorders still needs to be explored.

In basic research, in contrast, many researchers have proven that the acupuncture could be a useful therapeutic tool to alleviate addictive disorders. Han and his colleagues showed that that

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acupuncture was capable of alleviating morphine or heroine withdrawal syndromes (Han and Zhang, 1993). Recently, our results also showed that acupuncture attenuated the nicotine or cocaine-induced behavioral sensitization by modulating dopamine release or activation of postsynaptic dopamine receptors in the striatum or the nucleus accumbens (NAC) (Lee *et al.*, 2002; Chae *et al.*, 2004). Furthermore, acupuncture treatment inhibited alcohol withdrawal syndrome and increase of Fos-like immunoreactivity (FLI) in rats undergoing ethanol (Kim *et al.*, in preparation). In this paper, we will briefly review whether the acupuncture could affect drug addiction, such as nicotine, cocaine and alcohol and what is the mechanism underlying its action in the treatment of addictive disorders.

ACUPUNCTURE EFFECT ON ADDICTIONS

Nicotine addiction and acupuncture

The acupuncture on abstinence from smoking have been reported to be effective, and its effects were similar to those of the nicotine chewing gum and the behavior therapy (Jiang and Cui, 1994). Evidences from clinical studies regarding effectiveness of acupuncture, however, are still controversial. Available meta-analyses of acupuncture failed to show efficacy in aiding smoking cessation (OR 1.08, CI 0.77-1.52 and OR 1.1, CI 0.7-1.6) (White *et al.*, 2002).

In animal study, we examined that acupuncture could affect on nicotine-induced behavioral locomotor activity and c-Fos expression in nucleus accumbens (NAC) and striatum (Chae *et al.*, 2004). A large body of evidence indicates that drug addiction is in part related with its effects on dopamine neurons in the reward pathways of the brain (Bradberry and Roth, 1989; Yoshimoto *et al.*, 1991; Dani and De Biasi, 2001). The behavioral and reinforcing effects of addictive drugs are mediated by central dopaminergic system, especially the mesolimbic system from the ventral tegmentum to the region of the limbic system concerned with emotionality and reward (Yoshimoto *et al.*, 1991; Dani and De Biasi, 2001). As with cocaine, amphetamines, and morphine, addiction to nicotine is believed to result from increased release of dopamine in the

region of NAC (Clark, 1990; Pidoplichko *et al.*, 1997). Nicotinic acetylcholine receptors are located throughout the central nervous system, but the neurons located in the ventral tegmental area (VTA) increase activity with nicotine administration and concurrently activate the increased release of dopamine into NAC (Pidoplichko *et al.*, 1997; Dani and De Biasi, 2001). Our results demonstrated that acupuncture at zusanli (ST36), but not control, significantly attenuated expected increase in nicotine-induced locomotor activity and FLI in the NAC and striatum to subsequent nicotine challenge (Chae, 2004). These findings suggest that acupuncture has a therapeutic effect on nicotine addiction, possibly by modulating postsynaptic neuronal activity in the NAC and the striatum.

According to the results above, we find out the possibilities that acupuncture could play key roles in nicotine addiction, and more vigorous trials are warranted to establish acupuncture's action in the treatment of smoking cessation in clinical trials.

Cocaine addiction and acupuncture

The general approach of the treatment industry has been to extend treatment methods that are ordinarily applied to cocaine abuse (Weddington, 1993). The limited success in treating this difficult addiction, however, has encouraged the investigation of other potentially effective methods of treatment (Gorelick, 1993). One of these is auricular acupuncture, which is the insertion of acupuncture needles into prespecified locations in the ear. Auricular acupuncture is widely used to treat cocaine addiction in the world. However, evidence from controlled studies regarding this treatment's effectiveness has not been consistent. One study showed that acupuncture was not more effective than a needle insertion or relaxation control in reducing cocaine use (Margoline *et al.*, 2002). Another study demonstrated that longitudinal analysis of the urine data for the intention to treat sample showed that patients assigned to acupuncture were significantly more likely to provide cocaine-negative urine samples relative to both the relaxation control (odds ratio, 3.41; 95% confidence interval, 1.33-8.72; $P=0.01$) and the needle-insertion control (odds ratio, 2.40; 95% confidence interval, 1.00-5.75; $P=0.05$) (Avants *et al.*, 2000).

Cocaine has been known to be a potent and widely abused psychostimulant that exerts its behavioral and neuropharmacological effects, which may be also mediated by the central dopaminergic systems (Bradberry and Roth, 1989). Many studies have demonstrated that the reinforcing effects of cocaine are related to blockade of the dopamine reuptake systems (Ritz *et al.*, 1990), and consequent increases in the binding of dopamine to its postsynaptic receptors (Caine *et al.*, 2002). For the animal studies for the acupuncture treatment, we reported that acupuncture at HT7 inhibited behavioral sensitization to systemic cocaine injection (Lee *et al.*, 2002). HT7 on the heart channel has been clinically used to treat mental and psychiatric disorders in Oriental Medicine (Chae *et al.*, 2004). It was also examined whether *Coptidis Rhizoma* (CR) and berberine (BER) herbal acupuncture at HT7 point (CR/H and BER/H) have therapeutic effects on the cocaine-induced neurochemical and behavioral sensitization with observing locomotor activity, the change of c-Fos and tyrosine hydroxylase (TH) expression, and extracellular DA release in the NAC. These results indicate that the inhibitory effects of cocaine-induced behavioral and neurochemical sensitization by CR/H and BER/H are closely associated with the reduction of presynaptic dopamine release, and postsynaptic neuronal activity in the NAC (Lee, in preparation).

These findings suggest that acupuncture shows promise for the treatment of cocaine dependence. Further study will be needed to examine its contribution to cocaine addiction in clinical trials.

Alcoholism and acupuncture

Acupuncture as a therapeutic intervention is also widely practiced in the treatment of alcohol abuse. A number of enthusiastic reports were published about the effectiveness of acupuncture in combating all forms of addiction. Speculations focused on acupuncture-triggered release of endogenous opiates, supposedly blocking the mechanisms involved in withdrawal and craving (Wen *et al.*, 1979). However, randomized controlled trials to support these speculations are scarce, particularly in alcohol addiction (ter Riet *et al.*, 1990). Trumpler *et al.* set out to determine the feasibility of this approach, and to perform a preliminary comparison of laser

and needle acupuncture with a sham intervention for alcohol withdrawal. The data from this pilot trial did not suggest a relevant benefit of auricular laser acupuncture for alcohol withdrawal. A larger parallel group trials with adequate sham interventions are needed, however, to reliably determine their effectiveness in this condition (Trumpler *et al.*, 2003).

Although there is a lack of well-controlled experiment investigating the effect of acupuncture on alcohol abuse, however, it has been recently shown that acupuncture suppressed alcohol-drinking behaviors in rats (Yoshimoto *et al.*, 2001). It was examined that acupuncture could modulate alcohol withdrawal syndrome (AWS) and FLI in the striatum and NAC of rats. During 3 days of cessation following chronic administration of ethanol, rats showed a significant increase in AWS, such as hypermotility, tail rigidity, grooming and tremor, and increase in FLI in the dopamine terminal areas in the brain. Treatment of acupuncture at ST36 or SP6 during withdrawal period inhibited AWS and expected increase in FLI of rat undergoing ethanol. These results suggest that acupuncture may be useful in treatment of alcoholism by modulating postsynaptic neural activation in the striatum and NAC (Kim *et al.*, in preparation).

Another study showed that the GABA_B receptor system played a modulatory role in the mesolimbic system in drug abuse, including ethanol (Yoon *et al.*, 2004). It was designed to investigate the effect of acupuncture on acute ethanol-induced dopamine release in NAC and the potential role of the GABA_B receptor system using microdialysis. Results showed that acupuncture at HT7, but not at control points (PC6 or tail) significantly decreased dopamine in NAC. The inhibitory effect of acupuncture on dopamine release was completely blocked by the GABA_B receptor antagonist SCH 50911. These results demonstrated that stimulation of specific acupoints could inhibit dopamine release in the NAC and implicate the GABA_B receptor system in the mechanism underlying acupuncture inhibition of dopamine release in NAC.

Therefore, these findings suggest that acupuncture has a therapeutic effect on alcohol addiction, possibly by modulating postsynaptic neuronal activity in the NAC and the striatum. In addition, rigorous and well designed clinical trials are also

warranted for elucidating acupuncture effects in alcoholism.

DISCUSSION

Acupuncture has been clinically used in the treatment of patients addicted to alcohol, smoking and other drugs of abuse. In general, acupuncture is known to be simple, economic, painless, and non-traumatic therapeutic methods, being able to inhibit the abstinence syndrome.

Addiction involves subtle changes in neurochemistry. Current research is focusing on various parts of the brain such as the NAC and VTA. A common feature for drugs of abuse, such as amphetamine, cocaine and opioids like morphine and heroin, is their activation of the mesolimbic dopaminergic neurons. Both amphetamine and cocaine increase dopamine concentrations in the nucleus accumbens by blocking its uptake through a transporter, whereas opioids may activate μ - or δ -opioid receptors on GABAergic interneurons in the VTA, thereby producing disinhibition and increased firing of the dopaminergic neurons. It is thought that chronic drug use induces long-term neuroadaptive changes within the mesolimbic dopaminergic system and leads to desensitization (tolerance) of the neural mechanisms that mediate reward, and sensitization to the behavioral actions of these drugs. This might contribute to compulsive drug-seeking behavior and relapse (Schenk *et al.*, 1998; Steiner *et al.*, 1999). This review suggest that the inhibitory effects of acupuncture on nicotine, alcohol, and cocaine may be mediated through the neuronal cells within the limbic structures, which are known to be involved in rewarding properties of drug abuse, rather than motor circuit. In addition, since the behavioral sensitization to nicotine, alcohol, and cocaine are closely associated with extracellular dopamine release or postsynaptic gene expression, dopamine release in the NAC and striatum, it is possible that acupuncture reduces development of locomotor activity by modulating dopamine release or activation of postsynaptic dopamine receptors in the striatum or the nucleus accumbens (Shim *et al.*, 2001).

In addition, the important next step in acupuncture research is to have a better understanding of the neurochemical mechanism of acupuncture in order

that the therapeutic effectiveness of acupuncture can be further increased. However, in the clinical studies, current evidence does not support the use of acupuncture for nicotine addiction, cocaine addiction, and alcoholism. Due to the paucity and poor-quality of the existing studies, a firm conclusion cannot be drawn. Also scientifically conducted clinical research is needed to examine the effectiveness of acupuncture for each disease or symptom that has been claimed to be treatable by acupuncture (George, 1998).

In conclusion, we found out the clues that acupuncture might play key roles in drug addiction and more rigorous clinical studies are also needed to define acupuncture's role in drug abuse.

REFERENCES

- Avants SK, Margolin A, Holford TR, Kosten TR. (2000) A randomized controlled trial of auricular acupuncture for cocaine dependence. *Arch. Intern. Med.* **160**, 2305-2312.
- Bradberry CW, Roth RH. (1989) Cocaine increases extracellular dopamine in rat nucleus accumbens and ventral tegmental area as shown by in vivo microdialysis. *Neurosci. Lett.* **103**, 97-102.
- Caine SB, Negus SS, Mello NK, Patel S, Bristow L, Kulagowski J, Vallone D, Saiardi A, Borrelli E. (2002) Role of dopamine D2-like receptors in cocaine self-administration: studies with D2 receptor mutant mice and novel D2 receptor antagonists. *J. Neurosci.* **22**, 2977-2988.
- Chae Y, Yang CH, Kwon YK, Kim MR, Pyun KH, Hahm DH, Lee HJ, Shim I. (2004) Acupuncture attenuates repeated nicotine-induced behavioral sensitization and c-Fos expression in the nucleus accumbens and striatum of the rat. *Neurosci. Lett.* **358**, 87-90.
- Clark PB. (1990) Mesolimbic dopamine activation-the key to nicotine reinforcement? *Ciba Found Symp.* **152**, 153-162.
- Dani JA, De Biasi M. (2001) Cellular mechanisms of nicotine addiction. *Pharmacol. Biochem. Behav.* **70**, 439-446.
- Gorelick D. (1993) Overview of pharmacologic treatment approaches for alcohol and other drug addiction: Intoxication, withdrawal, and relapse prevention. *Psychiatric Clinics of North America* **16**, 141-156.
- George A, Ulett, Songping Han, Ji-sheng Han. (1998) Electroacupuncture: Mechanisms and Clinical

- Application. *Society of Biological Psychiatry* **44**, 129-138.
- Han JS, Zhang RL. (1993) Suppression of morphine abstinence syndrome by body electroacupuncture of different frequencies in rats. *Drug Alcohol Depend.* **31**, 169-175.
- Jiang A, Cui M. (1994) Analysis of therapeutic effects of acupuncture on abstinence from smoking. *J. Tradit. Chin. Med.* **14**, 56-63.
- Kim JH, Chung JY, Kwon YK, Kim KJ, Yang CH, Hahm DH, Lee HJ, Shim I. Acupuncture reduces alcohol withdrawal syndrome and c-Fos expression in rat brain (In preparation).
- Lee B, Lee HJ, Hahm D, Shim I. Effect of herbal-acupuncture on repeated cocaine-induced behavioral and neurochemical sensitization in the rat (In preparation).
- Lee BB, Shim IS, Yang CH, Lee HI, Hahm DH, Lee HJ. (2002) Effect of acupuncture (HT7) on acute cocaine-induced locomotor activity and Fos-like immunoreactivity in the brain of the rats. *J. Kor Meridian and Acupoint.* **19**, 25-33.
- Lee H, Ernst E. (2004) Acupuncture for labor pain management; A systematic review. *Am. J. Obstet. Gynecol.* (in press)
- Margolin A, Kleber HD, Avants SK, Konefal J, Gawin F, Stark E, Sorensen J, Midkiff E, Wells E, Jackson TR, Bullock M, Culliton PD, Boles S, Vaughan R. (2002) Acupuncture for the treatment of cocaine addiction: a randomized controlled trial. *JAMA.* **287**, 55-63.
- NIH Consensus Conference. Acupuncture. (1998) *JAMA.* **280**, 1518-1524. Review.
- Otto KC. (2003) Acupuncture and substance abuse: a synopsis, with indications for further research. *Am. J. Addict.* **12**, 43-51.
- Pidoplichko VI, DeBiasi M, Williams JT, Dani JA. (1997) Nicotine activates and desensitizes midbrain dopamine neurons. *Nature* **390**, 401-404.
- Ritz MC, Cone EJ, Kuhar MJ. (1990) Cocaine inhibition of ligand binding at dopamine, norepinephrine and serotonin transporters: a structure-activity study. *Life Sci.* **46**, 635-645.
- Schenk S, Partridge B, Shippenberg TS. (1999) U69593, a kappa-opioid agonist, decreases cocaine self-administration and decreases cocaine-produced drug-seeking. *Psychopharmacology.* **144**, 339-346.
- Shim I, Javaid JI, Wirtshafter D, Jang SY, Shin KH, Lee HJ. (2001) Nicotine-induced behavioral sensitization is associated with extracellular dopamine release and expression of c-Fos in the striatum and nucleus accumbens of the rat. *Behav. Brain Res.* **121**, 137-147.
- Steiner H, Gerfen CR. (1998) Role of dynorphin and enkephalin in the regulation of striatal output pathways and behavior. *Exp Brain Res.* **123**, 60-76.
- Sytinsky I, Galebskaya L. (1979) Physiolo-biochemical basis of drug dependence treatment by acupuncture. *Addictive Behavior* **4**, 137-141.
- ter Riet G, Kleijnen J, Knipschild P. (1990) Acupuncture and chronic pain: a criteria-based meta analysis. *J Clin Epidemiol.* **43**, 1191-1199.
- Trumpler F, Oez S, Stahl P, Brenner HD, Juni P. (2003) Acupuncture for alcohol withdrawal: A randomized controlled trial. *Alcohol & Alcoholism* **38**, 369-375.
- Weddington W. (1993) Cocaine. Diagnosis and treatment. *Psychiatric Clinics of North America* **16**, 87-95.
- Wen LZ, Cheung SYC. (1973) Treatment of drug addiction by acupuncture and electrical stimulation. *Asian J. Med.* **9**, 138-141.
- Wen H, Ho W, Ling N, Ma L, Choa G. (1979) The influence of electroacupuncture on naloxone-induced morphine withdrawal? Elevation of immun-assayable beta-endorphin activity in brain but not in blood. *Am. J. Chin. Med.* **7**, 237-239.
- White AR, Rampes H, Ernst E. (2002) Acupuncture for smoking cessation. *Cochrane Database Syst Rev.* CD000009.
- Yoon SS, Kwon YK, Kim MR, Shim I, Kim KJ, Lee MH, Golden GT, Yang CH. (2004) Acupuncture-mediated inhibition of ethanol induced dopamine release in the rat nucleus accumbens through the GABA_B receptor. *Neurosci. Lett.* (in press)
- Yoshimoto K, Kato B, Sakai K, Shibata M, Yano T, Yasuhara M. (2001) Electroacupuncture stimulation suppresses the increase in alcohol-drinking behavior in restricted rats. *Alcohol Clin. Exp. Res.* **25**, 63-68.