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Research article

Acupuncture suppresses intravenous methamphetamine self-administration through GABA receptor's mediation

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ABSTRACT

Objectives: Methamphetamine is one of the widely abused drugs. In spite of a number of studies, there is still little successful therapy to suppress the methamphetamine abuse. Acupuncture has shown to attenuate the reinforcing effects of psychostimulant. Based on, the present study investigated if acupuncture could suppress intravenous methamphetamine self-administration behavior. In addition, a possible neuronal mechanism was investigated.

Materials & methods: Male Sprague-Dawley rats weighing 270–300 g were trained to intake food pellet. After catheter implantation, animal was trained to self-administer methamphetamine (0.05 mg/kg) intravenously using fixed ratio 1 schedule in daily 2 h session during 3 weeks. After training, rats who established baseline (infusion variation less than 20% of the mean for 3 consecutive days) received acupuncture treatment on the next day. Acupuncture was performed at each acupoint manually. In the second experiment, the selective antagonists of $GABA_A$ or $GABA_B$ receptor were given before acupuncture to investigate the possible neuronal involvement of GABA receptor pathway in the acupuncture effects. C-Fos expression was examined in the nucleus accumbens to support behavioral data.

Results: Acupuncture at HT7, but not at control acupoint LI5, reduced the self-administration behavior significantly. Also, the effects of acupuncture were blocked by the GABA receptor antagonists. C-Fos expression was shown to be parallel with the behavioral data.

Conclusions: Results of this study have shown that acupuncture at HT7 suppressed methamphetamine self-administration through GABA receptor system, suggesting that acupuncture at HT7 can be a useful therapy for the treatment of methamphetamine abuse.

1. Introduction

Methamphetamine, a widely abused drug, is mainly used as a psychostimulant although it is occasionally used at low doses for medical purposes, such as in attention deficit or hyperactivity disorder [7]. In the mesolimbic system of the brain, dopaminergic neurons projecting from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) are thought to play a pivotal role in the rewarding effects of abused drugs. Methamphetamine administration results in increased dopamine (DA) release in the NAc, known as the reward center; this increase in DA levels is responsible for the reinforcing effects of the psychostimulant, driving individuals to abuse [8,19].

Acutely, methamphetamine tends to reduce appetite and increase motor activity, respiration, heart rate, and body temperature. Chronic administration induces a number of psychiatric problems, such as anxiety, confusion, insomnia, loss of memory, and aggressive behavior. Cardiomyopathy and decreased immune function are also associated with methamphetamine use [21,28]. In addition, the chronic use of methamphetamine produces structural and functional changes in the brain. Therefore, the development of an innovative treatment for methamphetamine abuse is urgently needed [26].

Acupuncture, a traditional therapy practiced in eastern Asia, has

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been gaining interest as a useful treatment for drug addiction [1,2]. Indeed, a lot of studies have demonstrated that acupuncture is effective in suppressing the reinforcing effects of abused drugs such as cocaine, nicotine, morphine, and alcohol [3,5,6,9–17,20,23,29,30,32]. Notably, one study showed that acupuncture attenuated hyper locomotor activity and abnormal c-Fos gene expression in the NAc induced by acute methamphetamine administration [6]. In addition, acupuncture has shown to suppress the behavioral sensitization and conditioned place preference induced by methamphetamine, with regulating the levels of dopamine, tyrosine hydroxylase and monoamine oxidase in the NAc [8]. This suggests that acupuncture may have a suppressive effect on methamphetamine abuse.

However, a few studies only have examined the effectiveness of acupuncture in methamphetamine abuse. Furthermore, the effectiveness of acupuncture on intravenous methamphetamine self-administration has not been investigated. Therefore, this study examined whether acupuncture could inhibit methamphetamine use by employing an intravenous self-administration paradigm. In addition, the possible neuronal mechanism underlying the effects of acupuncture was investigated, focusing on the gamma aminobutyric acid (GABA) pathway.

2. Materials and methods

2.1. Animals

Male Sprague-Dawley rats (Daehan Animal, Seoul, Korea) weighing 270–300 g at the beginning of the experiment were used. Rats were housed in the environment of 12 h light-dark cycle (turn on at 7:00 a.m.), room temperature (22 ± 2 °C), and humidity (60 ± 2%). They were allowed to freely access to the food and water. Rats were treated under minimized stress cross over all of the experiments in compliance with the protocols approved by the Institutional Animal Care and Use Committee at Daegu Haany University.

2.2. Apparatus

Animals self-administered food and methamphetamine in the operant chambers sound-attenuated and ventilated (Med Associates, St. Albans, VT, USA). House lights were turned on at the start and turned off for 15 s when animals pressed the active lever. Cue lights were illuminated for 5 s when the rats pressed active lever and were extinguished. After turning off of the cue lights, rats spent 10 s in darkness (time out, TO). When animal pressed active lever, signal was delivered to the computer installed with experimental program (Schedule manager, Med Associates). Then, the motor pump located beside the chamber pushed the syringe and the methamphetamine solution was delivered to the rat passing swivel.

2.3. Food self-administration training

Animals were subjected to press active lever under a fixed ratio (FR) 1 schedule to obtain 100 food pellets (45 mg, Bio-serve, Frenchtown, NJ, USA) within 3 h. The house light remained turned off and cue light was illuminated all the time. Food training was performed once a day, and animals received food restriction (allowed 70% of daily taking) to facilitate learning the criteria. Animal who had succeeded in food training for 3 consecutive days was subjected to the surgery.

2.4. Surgery

Animals that had passed food training were allowed to freely take the food. Rats were anesthetized with sodium pentobarbital (50 mg/kg, i.p.). Chronic silastic catheters (Dow Corning, Midland, MI, USA; 0.02″ ID × 0.037″ OD) were surgically implanted into the jugular vein and fixed with mersilene surgical mesh (Ethicon Inc., Somerville, NJ, USA). The catheter was exteriorized through the back of rat using 22 gauge guide cannula (Palstics One, Roanoke, VA, USA). Silastic tubing and guide cannula were embedded with dental cement. During recovery period, 0.2 ml of saline containing heparin (30 U/ml) was daily flushed into the catheter to maintain patency.

2.5. Methamphetamine self-administration training

Following recovery period of at least 1 week, animals were subjected to self-administer methamphetamine (0.05 mg/kg; Sigma-Aldrich, St. Louis, MO, USA). 0.2 ml of saline containing heparin (30 U/ml) was flushed into the catheter immediately before and after each session. When rats press the active lever, 0.1 ml of methamphetamine solution was infused. The response of inactive lever was recorded but made no result. Methamphetamine self-administration training was performed under FR 1 schedule for 3 weeks using daily 2 h session. Thereafter, if animals had shown the stable infusion numbers for 3 consecutive days (variation less than 20% of the mean of the 3 days) the mean of infusion number was regarded as baseline.

2.6. Acupuncture treatment

Animals who had established baseline received acupuncture treatment on the next day. Acupuncture was performed for 1 min at bilateral acupoints immediately before the test session. Stainless-steel needles (diameter 0.18 mm, length 8 mm, Dongbang Acupuncture Inc., Chingdao, China) were inserted vertically into a depth of 2–3 mm at each acupoint. Stimulation was delivered by bi-directional twisting needle at a frequency of twice per sec for a total of 2 s at the moment of inserting and withdrawal. Acupuncture treatment was performed in awaken under a slight movement restriction. Daily handling was given for 2–3 min across all experiments to minimize the stress from the movement restriction.

2.7. Experimental design

2.7.1. The first experiment

Rats of HT7 group (n = 8) received acupuncture at HT7 located on the transverse crease of the wrist of the forepaw, radial to the tendon of the muscle flexor carpi ulnaris [31]. Rats of LI5 group (n = 8) received acupuncture at LI5 located on the posterolateral aspect of the wrist, at the radial side of the dorsal wrist crease, distal to the radial styloid process, in the depression of the anatomical snuffbox [31]. Rats of control group (n = 8) received the same treatment with acupuncture groups without needle stimulation. The anatomical locations of acupoints were determined according to those in animal acupuncture atlas [27] and our previous studies [13,15,17,29]. Treatments were assigned using counter balance design.

2.7.2. The second experiment

Animals that had established baseline were assigned into following 6 groups: control group (n = 6) and HT7 group (n = 6) were given the same treatment with the first experiment, respectively; HT7 + bicuculline (BIC) group (n = 6) received acupuncture at HT7 and pretreatment of BIC (Tocris, Ellisville, MO, USA; 1 mg/kg; 30 min prior to acupuncture), the selective $GABA_A$ receptor antagonist; HT7 + SCH 50911 (SCH) group (n = 6) received acupuncture at HT7 and pretreatment of SCH (Tocris, 2 mg/kg; 30 min prior to acupuncture), the selective $GABA_B$ receptor antagonist; BIC group (n = 6) and SCH group (n = 6) were given intravenous injection of BIC and SCH, respectively, without needle stimulation.

2.8. Immunofluorescence

In order to confirm the acupuncture effects using immunohistochemistry, c-Fos expression was examined. On the next day