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Acupuncture suppresses reinstatement of morphine-seeking behavior induced by a complex cue in rats

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HIGHLIGHTS

- Prevention of relapse is an important problem in the treatment of drug addiction.
- Acupuncture at SI5 attenuated the reinstatement of morphine-seeking behavior.
- Acupuncture at SI5 did not influence the food-taking and -seeking behavior.
- Acupuncture's suppression was inhibited by GABA receptor antagonists.
- Effect of acupuncture is mediated, at least in part, via GABA receptor system.

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ABSTRACT

Morphine causes physical and psychological dependence for individuals after repeated-use. Above all, our previous study showed that acupuncture attenuated reinstatement of morphine-seeking behavior induced by pharmacological cue. In this study, we investigated whether acupuncture could suppress the reinstatement of morphine-seeking behavior induced by the combination of environmental and pharmacological cues and the possible neuronal involvement. Male Sprague-Dawley rats were trained to self-administer morphine (1.0 mg/kg) for 3 weeks. Following the withdrawal phase (7 days), the effects of acupuncture on reinstatement of morphine-seeking behavior were investigated. For the investigation of neuronal involvement, the $GABA_A$ receptor antagonist bicuculline and the $GABA_B$ receptor antagonist SCH 50911 were pre-treated. Morphine-seeking behavior induced by combination of re-exposure to the operant chamber and morphine injection was suppressed perfectly by acupuncture at SI5, but not at the control acupoint LI5 and this effect was blocked by pre-treatment with the GABA receptor antagonists. This study suggests that acupuncture at SI5 can be considered as a predominant therapy for the reinstatement of morphine-seeking behavior in humans.

1. Introduction

Morphine, a widely used analgesic, enhances the dopamine (DA) release in the nucleus accumbens (NAc) of the mesolimbic system and may be addictive as a result [11]. This enhancement acts as positive reinforcement and contributes to drug-seeking and -taking behavior. Furthermore, repeated use of morphine may induce neuronal changes that lead to physical dependence and durg-seeking behavior [6,29,31].

Relapse is a critical problem for drug abusers, and treatment often focuses on the prevention of relapse. Relapse in animal models and humans is generally triggered by cues such as re-exposure to the drug or the drug-taking environment [27]. So, medication that helps prevent relapse must reduce the excitatory response to the cues.

Acupuncture, a type of Oriental medicine, has been recognized as an outstanding therapy for drug addiction [1,4,10,22]. Several preclinical studies have demonstrated that acupuncture normalizes opiate-induced behaviors [3,20,30,32] and abnormal Fos expression [15,21] and regulates DA release in the NAc in morphine sensitization [13]. Furthermore, acupuncture has been shown to attenuate withdrawal symptoms precipitated by naloxone [16]

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and reverse chronic morphine-induced neuronal morphological changes in the ventral tegmental area (VTA) [3,8]. Moreover, our previous studies have demonstrated that acupuncture can attenuate the reinforcing effects of morphine via gamma-aminobutyric acid (GABA) receptors [34].

In Oriental medicine, acupoint SI5 is known to ameliorate imbalance between Heart meridian and Small Intestine meridian and can be used to treat mental discomfort and emotional distress [5,24]. Choi et al. [2] reported that acupuncture at SI5 diminished locomotor activity and c-Fos expression in the striatum induced by acute methamphetamine. In addition, our research has extended previous findings by showing that acupuncture at SI5 suppresses the reinstatement of morphine-seeking behavior induced by injection in rats [17].

However, the factors contributing to the relapse in humans are complex and involve a mix of environmental and pharmacological cues. Therefore, a therapy must be useful for the complex cue. The present study investigated the possibility that SI5 acupuncture could prevent morphine-seeking behavior induced by a combination of environmental and pharmacological cues, and in addition, the possible neuronal involvement was investigated.

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. Animals were housed in a room with 12 h light–dark cycle (turn on at 7:00 a.m.) maintained at 22 ± 2 °C with 60% humidity and ad libitum access to food and water. All experimental procedures were in accordance with the Guidelines for Care and Use of Laboratory Animals of Daegu Haany University.

2.2. Apparatus

Morphine and food self-administration were carried out in the same operant conditioning chambers (Med Associates, St. Albans, VT, USA). House lights were turned on at the start of the session and extinguished for 15 s after rat pressed the active lever. Cue lights were illuminated when animals pressed the active lever and turned off after 5 s. After the 5 s, cue lights were extinguished and animals remained in darkness for 10 s until the turning on of the house light. Pressing the active lever produced infusion of morphine solution (0.1 ml) into the jugular vein of rats via Tygon tubing shielded by a metal spring and secured to a screw embedded in the catheter assembly.

2.3. Food training

Following habituation to the experimental environment for 3 days, animals were trained to press the active lever for 45 mg food pellets (Bio-serve, Frenchtown, NJ, USA) under a daily fixed ratio (FR) 1 schedule. Rats were required to obtain 100 food pellets within 3 h by spontaneously pressing the active lever. When animals had succeeded in obtaining 100 food pellets on 3 consecutive days, they underwent catheter implantation.

2.4. Catheter implantation

Under pentobarbital anesthesia (50 mg/kg, i.p.), chronic silastic catheters (Dow Corning, Midland, MI, USA; 0.02 in. ID × 0.037 in. OD) coated with tridodecylmethyl ammonium chloride (TDMAC) heparin (Polysciences Inc., Warrington, PA, USA) were surgically implanted into the right jugular vein and fixed using Mersilene surgical mesh (Ethicon Inc., Somerville, NJ, USA) [34]. The catheters were exteriorized at the back of rats using a 22 gauge guide cannulae (Palstics One, Roanoke, VA, USA) through the skin incision. Silastic tubing and guide cannulae were embedded in dental cement and secured using Prolene surgical mesh. A 0.2 ml solution of saline containing heparin (30 U/ml) was flushed into the catheter daily to maintain the patency throughout the experiment.

2.5. Morphine self-administration

Following recovery period of 1 week, animals were trained to self-administer morphine hydrochloride (JEIL Pharmaceutical Co. Ltd., Daegu, Korea) dissolved in sterilized saline. When animal pressed the drug-paired lever (active lever), 0.1 ml of morphine (1.0 mg/kg) was delivered through jugular catheter for 5 s. Response to the inactive lever was recorded with no consequence. During the morphine infusion, the house light was turned off, and the cue light above the active lever was illuminated, followed by 10 s "time-out" (TO) period during which both the house and cue lights were off. Responses during the TO were recorded but had no consequence. Morphine self-administration training was carried out under FR 1 schedule with daily 2 h session. Following 3 weeks of morphine self-administration, animal that exhibited a stable morphine infusion (baseline, <20% variation from the mean on the last 3 days) underwent the withdrawal phase.

2.6. Withdrawal

Morphine abstinence was achieved by confining the animals to their home cage as previously described [28]. This withdrawal method was designed to advance from our previous study [17] in which we used pharmacological cue only, by using more complex cue of the combination of pharmacological and environmental cues. Following the 1-week withdrawal phase, a reinstatement test was performed on the next day.

2.7. Reinstatement

For the reinstatement, rats were re-exposed to the operant chamber and received a priming injection of morphine (0.25 mg/kg, i.v.). The injection was administered immediately prior to the test session, and the dose of morphine was determined according to a preliminary experiment on the dose response. During the test session, morphine was replaced by saline.

2.8. Acupuncture

Acupuncture was given bilaterally at each acupoint for 1 min immediately prior to morphine injection, as previously described [16,34]. Stainless-steel needles (Dongbang Acupuncture Inc., Chingdao, China) with a diameter of 0.18 mm and a length of 8 mm were inserted vertically into a depth of 2–3 mm, and stimulation was produced using bi-directional twisting of the needle at a frequency of twice per sec for a total of 2 s on the insertion and withdrawal from acupoints. Movement was restricted during acupuncture, which was performed without anesthesia. All animals were habituated to daily handling for 2–3 min throughout the experiment to minimize stress following acupuncture.

2.9. Experimental design

2.9.1. Experiment 1

Following the withdrawal period, animals were randomly divided into four groups: control, SI5, ST36, and LI5. The SI5 group