Research article

Music therapy inhibits morphine-seeking behavior via GABA receptor and attenuates anxiety-like behavior induced by extinction from chronic morphine use

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ABSTRACT

Rationale: Morphine is a representative pain killer. However, repeated use tends to induce addiction. Music therapy has been gaining interest as a useful type of therapy for neuropsychiatric diseases.

Objectives: The present study examined whether Korean traditional music (KT) could suppress morphine-seeking behavior and anxiety-like behavior induced by extinction from chronic morphine use and additionally investigated a possible neuronal mechanism.

Material & methods: Male Sprague-Dawley rats were trained to intravenously self-administer morphine hydrochloride (1.0 mg/kg) using a fixed ratio 1 schedule in daily 2 h session during 3 weeks. After training, rats who established baseline (variation less than 20% of the mean of infusion for 3 consecutive days) underwent extinction. Music was played twice a day during extinction. In the second experiment, the selective antagonists of GAB\textsubscript{A} and GAB\textsubscript{B} receptors were treated before the last playing to investigate the neuronal mechanism focusing on the GABA receptor pathway. Another experiment of elevated plus maze was performed to investigate whether music therapy has an anxiolytic effect at the extinction phase.

Results: KT but not other music (Indian road or rock music) reduced morphine-seeking behavior induced by a priming challenge with morphine. And, this effect was blocked by the GABA receptor antagonists. In addition, KT showed anxiolytic effects against withdrawal from morphine.

Conclusions: Results of this study suggest that KT suppresses morphine-seeking behavior via GABA receptor pathway. In addition, KT showed to have anxiolytic effects, suggesting it has bi-directional effects on morphine.

1. Introduction

Morphine is one of the most widely used pain killers [22]. Its analgesic effect is produced by enhancing the dopamine (DA) release in the nucleus accumbens (NAc) of mesolimbic system and this increase of DA release is caused by disinhibition of DA neuron through the inhibition of gamma aminobutyric acid (GABA) interneuron in the ventral tegmental area (VTA) [13]. However, this action tends to produce a reinforcing effect and drive individuals to addiction when repeatedly used [3,31]. In the course of the development of addiction, minimizing the craving or seeking for an abused drug during the extinction phase is thought to be critical, as reinstatement during abstinence makes it difficult to treat addicts. Therefore, medications developed to treat drug addiction have focused on reducing this DAergic enhancement in the NAc and indeed during the past decades, some effective chemicals were developed. Nevertheless, it remains difficult to treat morphine addiction.

Conversely, withdrawal or extinction from repeated morphine use results in DA depletion and tends to induce unpleasant status including anxiety-like behavior [14] or withdrawal syndrome [20].

Music therapy, a new complementary and alternative medicine, has been gradually gaining interests as a useful option in diverse fields including neuropsychiatric diseases such as autism spectrum disorder, eating disorders, and anxiety [4,5,11,32] although the exact underlying mechanisms have not yet been fully understood.

In addition, a shamanic journey combined with repetitive drumming increased immunoglobulin A level and relaxation as well as decreased arousal levels and dreamlike states [5,7,8]. Also, pain was alleviated by shamanic intervention [30]. Notably, Hegde [9] has elucidated the effectiveness of the Asian traditional music.

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However, it is still not easy to find research showing the efficacy of music therapy on morphine addiction.

Based on these situations, the present study investigated whether music therapy using Asian traditional music can suppress morphine-seeking behavior and anxiety-like behavior induced by extinction from chronic morphine. In addition, a possible neuronal mechanism related to the effect of music therapy was further 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. Rats were housed in an environmental condition 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 food and water. Following at least 3 days of adaptation period, animals were subjected to the experiments. 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 the Daegu Haany University.

2.2. Apparatus

2.2.1. Self-administration chamber

Animals self-administered food and morphine in the same ventilated operant chambers sound-attenuated with double cubicles of inner plastic and outer wood (Med Associates, St. Albans, VT, USA). Chambers were equipped with two lights in the operant chamber i.e. house light mounted on a wall and cue light above the active lever. The house lights were turned on at the start of each session and turned off for 15 s when animals pressed the active lever. Cue lights were illuminated for 5 s when the rats pressed the active lever and were extinguished after that. After turning off of the cue lights, rats spent 10 s in darkness. When animal pressed active lever, a signal was delivered to the computer installed with an experimental program (Schedule manager, Med Associates). Then, the motor pump located beside the operant chamber pushed the syringe and the morphine solution in the syringe was delivered to the jugular vein of the rats passing swivel and Tygon tubing according to the experimental program designed by the researcher. The Tygon tubing was shielded by a metal spring and extended from the swivel, being secured to a screw embedded in the catheter assembly on the back of animals.

2.2.2. Elevated plus maze (EPM)

The elevated plus maze (EPM) chamber was made of black acrylic and was comprised of four arms (50 cm long × 10 cm wide). Two open arms had high ledges of 0.5 cm and two closed arms had 40 cm high dark acrylic walls. The chamber was elevated 40 cm from the floor and light and was illuminated with 1.5–2.0 lx in the test room. When rats were placed onto the center of the EPM apparatus and the start button was clicked on the computer, time spent in each arm was measured automatically for 5 min by a video tracking camera (Ethovision, Netherlands) mounted on the roof. White noise was maintained constantly at 70 dB during all phases of the experiment. The chamber was cleaned with distilled water and was dried after each test [14].

2.3. Food self-administration training

Rats that had adapted to the experimental environment for 3 days were then subjected to the food self-administration. They were required to press the active lever for food pellets (45 mg, Bio-serve, Frenchtown, NJ, USA) with a fixed ratio (FR) 1 schedule. Rats were required to achieve 100 food pellets by spontaneously pressing the active lever within 3 h and there was not a time out. On the first day, rats were exposed to an over-night schedule to promote learning of the active lever press. Both the house light and the cue light were illuminated all the time. Food training was performed once a day and rats were given food restriction to 70% of daily consumption to facilitate learning of the acquisition criteria. When an animal had succeeded in obtaining 100 food pellets for 3 consecutive days, he was subjected to the intravenous catheter implantation surgery.

2.4. Surgery

Animals that successfully achieved 100 food pellets during 3 consecutive days were allowed free access to food and water for 3 days before the surgery. For surgery, animal was anesthetized with an intraperitoneal injection of sodium pentobarbital (50 mg/kg). Chronic silastic catheters (Dow Corning, Midland, MI, USA; 0.02” ID × 0.037” OD) were surgically implanted into the right jugular vein and fixed with mersilene mesh (Ethicon Inc., Somerville, NJ, USA). The catheter was threaded out through the back of the rat using 22 gauge guide cannula (Palstics One, Roanoke, VA, USA) through a skin incision. Silastic tubing and guide cannula were embedded with dental cement and were secured with Prolene surgical mesh. The 0.2 ml of saline containing heparin (30 U/ml) was flushed once a day into the catheter for the maintenance of patency during the recovery period [16–19].

2.5. Morphine self-administration

After surgery, animals underwent a recovery period of at least 1 week. Following recovery, animals were subjected to self-administration of morphine. 0.2 ml of saline containing heparin (30 U/ml) was flushed into the catheter immediately before and after each daily session to maintain the patency of the tubing. When rats pressed the active lever, the house light was extinguished and the cue light was illuminated for 5 s. During the 5 s, 0.1 ml of morphine solution (1.0 mg/kg) was infused. After 5 s of morphine infusion, animals underwent a “time-out” (TO) period of 10 s during which both the house light and the cue light were extinguished, and rats experienced darkness. Also, during the TO, both active and inactive lever responses were recorded but produced no consequences. Following the TO, the house light was turned on again. The responses of the inactive lever were recorded but made no consequence. Morphine self-administration training was performed under the FR 1 schedule for 3 weeks using daily 2 h session following a previous study [17]. Following morphine training, when animals had shown the stable infusion numbers for the last 3 days (variation less than 20% of the mean of the last 3 days), it was regarded as establishment of baseline [16–19].

2.6. Extinction and reinstatement

Animals who had established baseline, underwent an extinction period by substituting morphine with saline. After 1 week of extinction, morphine seeking behavior was induced by a priming injection of morphine (0.25 mg/kg) following previous studies [16,17].

2.7. Experimental design

2.7.1. Morphine self-administration

a The first experiment: effect of music therapy

After the extinction period, the animals were randomly divided into four groups. Rats of the Korean traditional music (KT) group (n = 7) listened to KT. Rats of the Indian (Native American) traditional music (IT) group (n = 7) listened to IT. Rats of the rock music (RM) group (n = 7) listened to RM. Control groups primed with saline (n = 7) and morphine (n = 7) were received the same treatment with music groups without music.

b The second experiment: neuronal involvement
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