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Repeated 2 Hz peripheral electrical stimulations suppress morphine-induced CPP and improve spatial memory ability in rats

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Abstract

Our previous studies have shown that 2 Hz peripheral electrical stimulation (PES) can suppress morphine-induced conditioned place preference (CPP) in the rat, although the mechanisms remain unclear. Since CPP involves the mechanism of learning and memory, it is rational to ask whether the suppressive effect of repeated 2 Hz PES on morphine-induced CPP is due to an impairment of the function of spatial learning and memory. Rats were trained with 4 mg/kg morphine, i.p. for 4 days to establish the CPP. Twenty-four hours after the CPP testing, they were given PES at 2 Hz once a day for 1, 3 or 5 days, followed by another CPP testing. The results showed that (1) the morphine-induced CPP was significantly inhibited by 3 or 5 consecutive sessions, but not by single session of 2 Hz PES. (2) A test of spatial leaning and memory ability using the Morris water maze task revealed that 2 Hz PES per se exhibited a promoting, rather than a deteriorating effect on the ability of spatial memory. (3) 2 Hz PES by itself produced a moderate yet significant CPP. The results imply that (a) a low frequency PES can produce a rewarding effect as revealed by the CPP testing, which may account, at least in part, for its suppressive effect on morphine induced CPP, (b) the suppressive effect of PES on morphine induced CPP is not due to a deteriorating effect on the ability of spatial memory.

Keywords: Peripheral electrical stimulation (PES); Conditioned place preference (CPP); Rewarding effect; Spatial learning and memory

Introduction

Classical manual acupuncture has been used in China for thousands of years. One of the recent technical development was to use peripheral electrical stimulation (PES) applied via the acupuncture needles inserted into the acu-points, so that electrical stimulation is used to replace the mechanical stimulation. The PES has been demonstrated to be a safe, gentle, low-cost and effective self-healing approach for treating various kinds of chronic and stubborn diseases such as pain of various causes (Ahmed et al., 2000; Carlsson, 2002; Chen and Han, 1992; Hamza et al., 2000; Humaidan and Stener-Victorin, 2004; Huang et al., 2002; Stener-Victorin et al., 2003a, 2004), neurodegenerative disorders (Gao et al., 2002; Lin and Lin, 2000; Pei et al., 2001; Scherder and Bouma, 1999; Scherder et al., 1995, 1998, 2000), coronary heart diseases (Meng, 2004), polycystic ovaries (Stener-Victorin et al., 2003b), and climacteric symptoms (Sandberg et al., 2002). PES has also been reported for the treatment of drug dependence, especially of opiate withdrawal syndrome (Fung et al., 1980; Malin et al., 1988; Shuaib, 1976; Ho et al., 1978; Wen et al., 1979). We have reported the efficacy of PES in treating heroin dependence in animals and humans, including physical and psychic dependence (Han and Zhang, 1993; Wu et al., 1999).

Conditioned place preference (CPP) is presumed to be a useful tool to test the efficacy of pharmacological or nonpharmacological interventions on the rewarding or reinforcing effects of drugs of addictive potency (Tzschentke, 1998). Recent work in our laboratory have shown that pretreatment with single-session PES of 2 Hz

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prior to the testing task could block or prevent the expression of morphine-induced CPP in rats (Wang et al., 2000). This finding provided the first evidence that the PES might possess an anti-craving activity. In the present study, experiments were designed to test whether single- or multiple-session of 2 Hz PES can block or abolish the already existing morphine-induced CPP in rats. Considering the possibility that the inhibitory effects of PES on morphine-induced CPP might be resulted from its deteriorating effects on the ability of learning and memory of the rats, experiments were performed to assess whether 2 Hz PES would affect the behavior on Morris water maze (MWM) task. Finally, experiments were designed to test whether 2 Hz PES per se has a rewarding effect.

Materials and methods

Subjects

Male Sprague–Dawley rats of 3 months old were obtained from the Beijing Experimental Animals Center, Beijing. They were housed four in a cage on a 12:12 hour light–dark cycle (lights on at 7:00 P.M.). All experiments were performed during the dark phase. Food and water were provided ad libitum. The experimental procedures were approved by the Committee on Animal Care and Use of the Peking University.

Drugs

Morphine hydrochloride (the First Pharmaceutical Factory of Shenyang, China) was dissolved in 0.9% saline to the final concentration of 4 mg/ml.

Conditioned place preference

Place conditioning was conducted in a three-compartment apparatus with an unbiased design. The apparatus was a black rectangular PVC box (75 × 22 × 30 cm) divided into three chambers separated by guillotine doors. The two end chambers (30 × 22 × 30 cm) used for conditioning were connected by a smaller center chamber (15 × 22 × 30 cm). The two end chambers were distinguished from each other in two ways. One had a group of 4 lights arranged in a square pattern on the end wall and a stainless steel mesh floor (1.3 × 1.3 cm^2), whereas the other had the lights arranged in a triangle form on the wall and a rod floor (1.3 cm apart) (Shi et al., 2003). The center chamber had gray walls and a smooth floor. Fifteen infrared beams spaced 5 cm apart were monitoring the motion of the rat. The Infrared sensors communicated to a computer every 100 ms through an interface. All experimental events were controlled and recorded automatically by the computer and the interface located in the same room. The computer also provided continuous white noise served to mask external sounds.

The CPP procedure consisted of three phases including pretest, conditioning and test. Prior to the start of experiment, the subjects were handled twice daily (at 8:00 A.M. and 2:00 P.M.) for 5 days. On the pretest day (Day 0), rats were placed individually in the center chamber with the guillotine doors removed. They were allowed to freely explore the entire apparatus for a 15-min session. The amount of time spent in each compartment was recorded automatically. Rats that spent more time (over 100 s) in one of the end chambers than the other were excluded from the experiment. Over the next 8 sessions (2 sessions per day) subjects received a double-alternating sequence of differential conditioning. In the morning, rats were injected with saline (1 ml/kg) and immediately placed in the compartment assigned as “non-drug” for 45 min. In the afternoon (6 h later), rats were injected with morphine at the dose of 4 mg/kg and placed in the compartment assigned as “drug”. The schedule was counter balanced in the next day, that is, morphine in the morning and saline in the afternoon. After each conditioning session, the rats were returned to their home cages and the entire apparatus was cleaned with alcohol wipes to minimize trapped odors. On the test day (Day 5), rats were tested under the conditions used for pretest without morphine or saline injection. The amount of time spent in each compartment was recorded to assess individual preference.

Morris water maze

The Morris water maze task was assessed in a water tank consisted of a circular black pool (diameter 120 cm, depth 60 cm), filled with 29 cm of water kept at a temperature of 24 ± 1°C. The pool was divided into four quadrants with an escape platform placed in one of the quadrants (the target quadrant). The escape platform was made of clear Plexiglas of 10 cm diameter, submerged 1 cm below the surface of the water, 25 cm apart from the pool-side. A video camera was mounted in the center above the circular pool and the movement of animals was pictured and the signals transmitted to a computer. Rats received two trials every day during seven daily acquisition sessions. Trial A was started by placing a rat into the pool, facing the wall of the tank. Each of the four starting positions (north, east, south and west) was used once in two consecutive trials; their order was randomized. A trial was terminated as soon as the rat had climbed onto the escape platform or when 60 s had elapsed. The rat was allowed to stay on the platform for 15 s. It was then taken from the platform and gently dried with a towel and returned to its home cage. Trial B was started approximately 2 hours later. The escape latency of each rat on each trial was automatically recorded by the computerized system. On the seventh day of training, the platform was removed from the pool and the rat was given one 60-s probe trial test. The time spent in each quadrant was recorded and expressed as a percentage of the total swimming time (60 s), respectively.