



Neuroprotection effects of retained acupuncture in neurotoxin-induced Parkinson's disease mice

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ABSTRACT

The aim of this study was to investigate the role of retained acupuncture (RA) in neurotoxin-induced Parkinson's disease (PD) mice. Male C57BL/6 mice were injected with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to induce the PD model. The mice were divided into four groups, namely, (1) normal; (2) MPTP + retained acupuncture (RA); (3) MPTP + electroacupuncture (EA); (4) MPTP + sham acupuncture (SA). After mice being manipulated with/without acupuncture at acupoints (Daling, PC 7), groups 2–4 were injected with MPTP (15 mg/kg/d). The mice were evaluated for behavioral changes, in terms of time of landing, after acupuncture treatment. The animals were sacrificed and their brains assayed for dopamine and its metabolites and tyrosine hydroxylase (TH) expression by using HPLC and immunohistochemistry/Western blotting, respectively. [¹²³I] IBZM-SPECT imaging between SA and RA groups were compared. The results showed that the time of landing of the three groups with treatment was significant longer than group 1 (normal) (4.33 ± 0.15 s). Nonetheless, group 2 (RA) (7.13 ± 0.20 s) had a shorter time of landing than group 4 (SA) (7.89 ± 0.46 s). The number of TH (+) neurons and the expression of TH proteins were significantly higher in the RA group than in the SA/EA groups. RA also increased the uptake of [¹²³I] IBZM into the striatum compared to the SA group. We conclude that RA possibly attenuates neuronal damage in MPTP-induced PD mice, which suggests RA may be useful as a complementary strategy when treating human PD.

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1. Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative disorders and affects about 1–2% of individuals over the age of 60 (Gasser, 2009). In Taiwan, it is estimated that the crude prevalence rate of idiopathic PD in persons aged 40 years and over is 706 per 100,000 individuals (Chen et al., 2009). PD is characterized by symptoms including rest tremors, postural instability, gait abnormality, bradykinesia and rigidity. The major pathological change of Parkinson's disease is a progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), the loss of striatal dopaminergic fibers, a dramatic reduc-

tion in the striatal dopamine levels and the presence of neuronal proteinaceous aggregates called Lewy bodies (LBs) (Schober, 2004).

The exact etiology of PD, though extensively studied, remains unknown. A number of factors including oxidative stress, mitochondrial dysfunction, inflammation and apoptosis have been implicated in the pathogenesis of PD (Mounsey and Teismann, 2010). Accumulating evidence suggests that exposure to environmental toxins and genetic aberrance lead to dopaminergic neuronal loss and clinical Parkinsonism (Fahn, 2010; Liang et al., 2003; Przedborski et al., 2001). Current clinical therapy for PD is largely based on a dopamine replacement strategy, primarily by administration of the dopamine precursor levodopa; however, this is often associated with the development of levodopa-related motor complications (Stowe et al., 2010; Tomlinson et al., 2010). Many different treatment strategies such as genetic and implant therapies have been evaluated for neuroprotection and neuroprevention in the laboratory and in a clinical context (Fu et al., 2006; Poewe, 2009), but the outcome is far from satisfactory.

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Since the 1990s the use of complementary and alternative medicine (CAM) worldwide has increased (Eisenberg et al., 1993). Therapies such as dietary supplements, vitamin therapy, exercise, physical therapy and massage therapy are reported to influence the symptoms of PD and/or the effectiveness of dopaminergic therapy (Zesiewicz and Evatt, 2009). Acupuncture therapy has been reported to show possible therapeutic effectiveness for PD in clinical trials, as manifested by an ameliorating of the clinical motor symptoms (Shulman et al., 2002) and an improvement in the quality of daily living (Zhuang and Wang, 2000); in addition acupuncture has no known interactions with other medication (Eng et al., 2006).

Previously, using functional magnetic resonance imaging (fMRI) and single photon emission computed tomography (SPECT), acupuncture analgesia has been shown to be a consequence of central modulation of the descending inhibitory pathway associated with pain sensation (Hsieh et al., 2001; Li et al., 2010; Wu et al., 2002). In human studies, activation of the hypothalamus has been identified as a cardinal finding of De-qi (Hsieh et al., 2001). Moreover, a recent fMRI study has suggested there is a cerebrocerebellar interaction during peripheral stimulation (Shih et al., 2009) and activation of the cerebellum can be visualized as occurring simultaneously with acupuncture treatment (Hsieh et al., 2001). This is indicative of an effect on the activation of extra-pyramidal system, an important area where the pathogenesis of PD occurs. Accordingly, it was our aim to investigate the effect of acupuncture on neurotoxin-induced PD mice.

2. Methods

2.1. Animals

Male C57BL/6 mice (National Laboratory Animal Center, Taiwan), 8 wk old, weighing 20–25 g, were housed in a temperature-controlled room under a 12-h light/12-h dark cycle (lights off from 8 p.m. to 8 a.m.). Food and water were provided *ad libitum* at all times. They were allowed to acclimate for at least 5 days before neurotoxin injection and were randomly assigned to different manipulation groups described below. The animals were treated under standardized conditions in accordance with “Guide for the care and use of laboratory animals” (Clark et al., 1996). This study was approved by the committee for the animal ethics of National Yang-Ming University. Around 150 mice were used in this study and animals being intolerable to MPTP treatment or anesthesia procedure were excluded.

2.2. PD model and study groups

The PD model was established by intraperitoneal injection of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) as described previously with some modifications (Cheng et al., 2008; Jackson-Lewis and Przedborski, 2007; Kurosaki et al., 2004). After two manipulations with/without acupuncture on the bilateral acupoints (Daling, PC 7), the mice were injected with MPTP hydrochloride (15 mg/kg/d) (Sigma, St. Louis, MO, USA) on five consecutive days to induce PD. To validate the neurotoxin-induced PD model, various doses of MPTP (0, 7.5, 15, 30 mg/kg/d) were injected intraperitoneally into the mice for five consecutive days, followed by model validation by behavior change and immunohistochemistry as mentioned below.

Acupuncture treatment was administered on day 3 and day 6 before the first MPTP injection and day 1 after the last MPTP injection (Fig. 1). Under adequate anesthesia with ether, the mice were manipulated with/without acupuncture by inserting two fine needles into both sides of the acupoint (Daling, PC 7) to a depth of 2–3 mm (Chiu et al., 2003; Ho et al., 2008). Since there are no

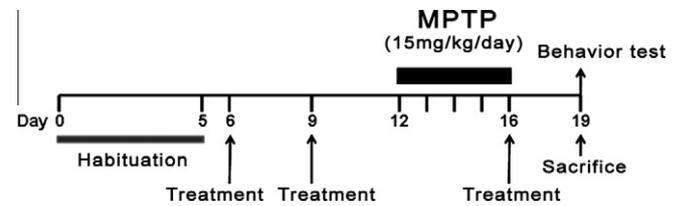


Fig. 1. Protocols for acupuncture manipulation of the MPTP-induced Parkinson's disease (PD) mice.

definite acupoints commonly used in treatment of human PD, we chose PC 7 just because previous study demonstrated an elevation of dopamine levels in the corpus striatum after EA stimulation on bil. Daling (PC 7) (Shen and Lai, 2007). According to our previous functional magnetic resonance imaging (fMRI) study (Chiu et al., 2003), the definition of acupuncture classification was (1) EA, acupuncture with electric stimulation (2 and 15 Hz, alternatively, 15 min, 1 mA) using an electrical nerve stimulator (Han Acutens, LH 202H, Taipei, Taiwan); (2) RA, acupuncture with needles left 2–3 mm in the acupoints without electric stimulation for 15 min; (3) SA, acupuncture with needles left just beneath superficial skin layer (Fig. 2). The mice were then divided into four groups, namely: group 1, normal mice; group 2, mice receiving MPTP + retained acupuncture treatment (RA); group 3, mice receiving MPTP + electroacupuncture treatment (EA) and group 4, mice receiving MPTP + sham acupuncture treatment (SA). For the control, the group 1 mice were injected with physiological saline at the same time points as the other groups.

Clinical studies suggested that serotonin-2 (5-HT₂) receptor antagonists may be useful in the treatment of the motor symptoms of PD (Ferguson et al., 2010). Therefore, in further experiments and in order to investigate the mechanism of any acupuncture effect on dopaminergic neurons, the 5-HT₂ receptor blocker SB206553 (5 mg/kg, dissolved in saline with 0.4% acetic acid, Tocris, Bristol, UK) was administered 1 h prior to each acupuncture treatment.

2.3. Behavioral test

The pole test was performed to detect the degree of bradykinesia at baseline for training (before MPTP treatment) and on the 3rd day after final MPTP administration. In brief, a vertical wooden pole (diameter 0.8 cm, height 50 cm) was wrapped in gauze to prevent slipping. The mouse was placed head upside by sliding its forepaws on top of the pole. The time from it turning nose down until it landed on the floor was measured. Each mouse was required to perform three successive trials at 5 min interval. All

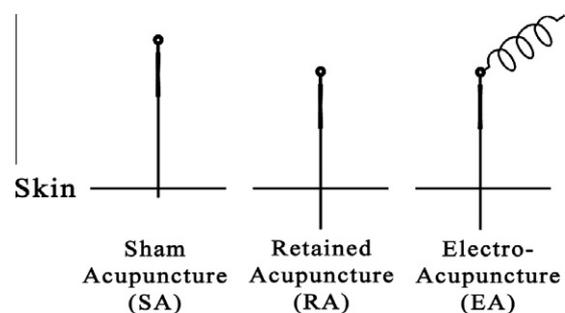


Fig. 2. Schematic presentation of acupuncture manipulation. The definition of acupuncture classification was (1) EA, acupuncture with electric stimulation (2 and 15 Hz, alternatively, 15 min, 1 mA) using an electrical nerve stimulator (Han Acutens, LH 202H, Taipei, Taiwan); (2) RA, acupuncture with needles left 2–3 mm in the acupoints without electric stimulation for 15 min; (3) SA, acupuncture with needles left just beneath superficial skin layer.

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